Archives of Neurology and Psychiatry

VOLUME 38 AUGUST 1937 NUMBER 2

PROGNOSTIC FACTORS IN SPONTANEOUS SUBARACHNOID HEMORRHAGE

ISRAEL STRAUSS, M.D.
AND
SIDNEY TARACHOW, M.D.
NEW YORK

The thesis of this paper is that spontaneous subarachnoid hemorrhage is a syndrome which may occur in a variety of pathologic states and that the prognosis varies with that of the underlying or associated pathologic process.

One hundred and five cases were studied, with an effort to find the incidence of systemic or local disease, cardiorenal vascular disease, acute or chronic infections and blood dyscrasias and also features which might lead one to suspect congenital cerebral aneurysm.

Clinically, the material can be divided roughly into two parts: (1) patients who died and (2) patients who survived. The first group is further subdivided into : (*a*) those who died on the first admission to the hospital and (*b*) those who recovered but died subsequently. The second group consists of: (*a*) those who recovered but were not followed after discharge; (*b*) those who recovered, had no recurrence and were followed for less than one year; (*c*) those who recovered, had no recurrence and were followed for from one to over eight years, and (*d*) those who had previous or subsequent attacks, either proved or presumptive, and recovered.

A tabular arrangement of the entire series follows:

	1 a	1 b	2 a	2 b	2 c	2 d	
	Died on First Admission	Died Subsequently	Improved, Not Followed	Improved, Followed Less Than 1 Year	Improved, Followed 1 to 8 Years	Improved, Recurrence	Total Number of Patients
Cardiorenal vascular disease	14	5	6	5	7	2	39
Tumor of the brain clinically	6	5	..	2	..	..	13
Subacute bacterial endocarditis	5	..	1	..	..	..	6
Cerebrospinal syphilis or history of syphilis	3	1	..	1	..	..	5
Blood dyscrasias	3	1	..	..	..	..	4
Clinical association with tuberculosis	2	..	1	..	..	..	3
Associated with diabetes	2	..	..	..	..	..	2
Associated with epilepsy	..	..	2	..	..	..	2
Associated with acute glomerulonephritis	..	..	1	..	..	..	1
No clinically discoverable disease	4	2	4	5	6	9	30
Total number of patients	39	14	15	13	13	11	105

From the neurological service of Dr. Israel Strauss, attending neurologist, the Mount Sinai Hospital.

The material will be considered from two aspects: (1) the mortality and life expectancy and (2) the underlying disease.

The patients who died on their first admission showed clinical signs of disease as follows (the verification at necropsy is also listed):

Clinical Signs		Observations at Necropsy
Cardiorenal vascular disease.....	14	6 (2 with aneurysms)
Tumor of the brain.....	6	5 (1 with aneurysm without arteriosclerosis)
Subacute bacterial endocarditis...	5	2 (All with positive blood cultures)
Syphilis.....	3	2 (2 with aneurysm and cerebrospinal syphilis)
Blood dyscrasias.....	3	3
Association with tuberculosis.....	2	0
Association with diabetes.....	2	2 (1 with pulmonary tuberculosis and 1 with congenital aneurysm)
No clinical disease.....	4	2 (aneurysm with cerebral arteriosclerosis)

More detailed information is contained in the accompanying tables. Information given in these tables will be listed as to sex, age, historical evidence pointing to underlying disease, blood pressure, clinical evidence pointing to underlying disease, spinal fluid findings, course of the illness and evidence at necropsy. In table 1 are listed patients with vascular disease who died on their first admission to the hospital.

This is the largest single group of cases in the entire series. The ages varied from 40 to 74 years, with a median of 50. Readings of blood pressure varied from 130 systolic and 80 diastolic to 270 systolic and 120 diastolic, with a median of 170 systolic and 108 diastolic.

Table 2 shows the group in which historical and clinical evidence pointed to tumor of the brain. Since in case 18 verification was not made by either surgical means or necropsy, the clinical history and findings will be presented in detail.

CASE 18.—A policeman aged 31 was admitted to the hospital with the chief complaints of numbness and weakness of the left side of the body. There had been an injury to the head with loss of consciousness nine years before and a laceration of the scalp unaccompanied by disturbance of consciousness one year before. Six months before his admission the patient began to complain of progressive, constant numbness over the entire right half of the body, including the head, and tinnitus and slight impairment of hearing on the left. He began to feel fatigued. One month later he commenced to drag the left leg and had headache and occasional dizziness. Two months before his admission he began to suffer from marked weakness, projectile vomiting, diplopia, dysarthria and dysphagia. At this time he entered another institution, where it was noted that he was irrational, overproductive and disoriented. He experienced hallucinations and delusions. Plates of the skull showed that the clinoid processes were bridged but not atrophic. There was a plaque of calcification in the falx, at the posterior frontal region. A ventriculogram showed slight symmetrical dilatation of the lateral ventricles. The third ventricle was enlarged, though narrow in its ventrodorsal diameters. The basilar cisterns were normal. An encephalogram showed that the aqueduct of Sylvius was displaced posteriorly in its distal portion. The fourth ventricle was not seen. There was air in the left side of the cisterna pontis, but none in the right. The patient received nine roengten treatments.

On admission to the Mount Sinai Hospital, the patient was apathetic and retarded, though the sensorium seemed clear. The pupils were unequal, the left

TABLE 1.—*Data on Patients with Cardiorenal Vascular Disease Who Died on First Admission*

No.	Sex; Age, Yr.	Historical Evidence	Blood Pressure	Clinical Findings	Spinal Fluid	Issue; Anatomic Observations
1	M 48	Hypertension 12 years	220/120	Generalized arteriosclerosis; enlarged heart; urine : albumin +	Uniformly bloody	Died in 8 hours; no autopsy
2	F 47	Hypertension, duration ?	270/120	Urine : albumin +, white and red cells	Uniformly bloody	Died on day of admission; autopsy showed cerebral arteriosclerosis, occlusion of posterior cerebellar artery, encephalomalacia and subarachnoid hemorrhage
3	M 44	None	140/ 80	Chronic nephritis; enlarged heart; urine : albumin +, casts	Uniformly bloody	Died in 4 days; no autopsy
4	F 65	Pulmonary mass 2 years	.....	Tumor of lung	Uniformly bloody	Died; no autopsy of brain; generalized arteriosclerosis; benign fibroma of lung; chronic bronchitis
5	F 48	Hypertension 8 years	172/108	Arteriosclerosis; enlarged heart; chronic glomerulonephritis	Xanthochromic, containing red cells	Died in 11 days; no autopsy
6	M 64	None	170/100	Generalized arteriosclerosis; cataracts; arcus senilis	Uniformly bloody	Died first day; no autopsy
7	F 74	None	140/ 65	Arteriosclerosis of retinal vessels; blood urea 40 mg.; blood sugar 180 mg.	Uniformly bloody	Died first day; no autopsy
8	M 60	Two previous vascular accidents leading to hemiparesis	190/110	Generalized arteriosclerosis	Uniformly bloody	Died in 15 days; no autopsy
9	M 52	None	130/ 80	Generalized arteriosclerosis	Uniformly bloody	Died in 2 days; no autopsy
10	M 52	None	150/100	Generalized arteriosclerosis	Uniformly bloody	Died in 3 days; autopsy cerebral atherosclerosis, encephalomalacia, encephalorrhagia, with oozing into subarachnoid space
11	M 40	Occasional headache	205/130	Narrow arteries in fundus	Xanthochromic; many red cells	Died in 12 days; no autopsy
12	M 40	None	150/110	Treatment for possible meningococcic meningitis	Variable; grossly bloody before death	Died; autopsy: cerebral arteriosclerosis, aneurysm of basilar artery
13	F 43	Cardiac disease and dependent edema	170/105	Narrow retinal arteries	Uniformly bloody	Died; autopsy: cerebral arteriosclerosis subarachnoid hemorrhage but no aneurysm
14	F 54	Hypertension 12 years	210/140	Normal	Uniformly bloody	Died; autopsy: cerebral arteriosclerosis, aneurysm of right middle cerebral artery

being larger than the right. The lateral and medial movements of the right eyeball were diminished. There was bilateral impairment of upward gaze. Nystagmus occurred to both sides but was greater to the left. There were fulness of the veins in the fundus bilaterally and slight elevation of the right optic disk. There were questionable central facial weakness on the right and impairment of hearing of the nerve type on the same side. There were ataxia and hemiparesis on the left. Touch, pain, temperature and position sense and stereognosis were lost on this side. Vibration sense was severely impaired on the left.

TABLE 2.—*Data on Patients with Evidence of Tumor of the Brain Who Died on First Admission*

No.	Sex; Age, Yr.	Historical Evidence	Blood Pressure	Clinical Findings	Spinal Fluid	Issue, Anatomic Observations
15	F 38	Diagnosis of subarachnoid hemorrhage 4 months previously on basis of xanthochromic fluid; subsequently diagnosis of tumor	130/72	Tumor of brain	Greenish; 1 cell	Operation; autopsy: hemorrhagic sarcoma
16	M 30	Venereal disease (?); glands in neck palpable	114/80	Tumor of brain	Uniformly pink	Died; autopsy: multiple hemorrhagic cystic tumors
17	F 4	Progressive; twitching, paresis, headache, vomiting and convulsions	.....	Tumor of brain suggested	Uniformly bloody	Died; autopsy: spongioblastoma with rupture into ventricle
18	M 31	Slow progressive	110/70	Tumor of brain	Xanthochromic; grossly bloody on occasion	Died; no autopsy
19	M 3	Previous nephrectomy for removal of tumor	.....	Normal	Normal	Died; autopsy: metastatic carcinoma to brain, subarachnoid hemorrhage
20	F 30	Suggested neoplasm of posterior fossa; ventriculography; stupor	110/68	Tumor of brain suggested	Repeated xanthochromia	Died; autopsy: aneurysm of posterior cerebral artery with thrombosis and recanalization, degenerative and proliferative changes in wall of aneurysm but no signs of cerebral arteriosclerosis

Spinal puncture showed 210 red cells and slight xanthochromia. Serologic reactions were negative. Five days after his admission the patient passed into deep stupor. Spinal tap showed grossly bloody fluid. The temperature rose to 103 F., and the patient died. No autopsy was permitted.

We believe that a diagnosis of intramedullary tumor of the brain stem is justified in this case.

Case 19 is included, even though there were never clinical evidences of subarachnoid hemorrhage. The observation of subarachnoid hemorrhage was definite at autopsy. Case 20, surprisingly, was that of a congenital aneurysm of the posterior cerebral artery, but it is included in this group because, for all purposes, the problem in the clinical manage-

ment of the illness was essentially that of tumor of the brain. No especial correlation is to be noted in the age grouping. The ages varied from 3½ to 38 years, with a median of 30.

In table 3 are reported cases of proved subacute bacterial endocarditis. The subarachnoid hemorrhage was undoubtedly symptomatic, and in two cases, terminal. Postmortem verification in two cases showed a ruptured mycotic aneurysm. The clinical picture of a sudden, severe meningeal syndrome in case 23 left no doubt as to the presence of sub-

TABLE 3.—*Data on Patients with Subacute Bacterial Endocarditis Who Died on First Admission*

No.	Sex; Age, Yr.	Historical Evidence	Blood Pressure	Clinical Findings	Spinal Fluid	Issue; Anatomic Observations
21	M 27	5 months	104/44	Chronic rheumatic heart disease; Streptococcus viridans by culture; subacute bacterial endocarditis	Uniformly bloody	Died; no autopsy
22	F 21	Rheumatic fever at age of 8 years, history for 9 months	125/65	Streptococcus viridans by culture; subacute bacterial endocarditis; terminal subarachnoid hemorrhage	Uniformly bloody	Died; no autopsy
23	F 10	14 months	.....	Streptococcus viridans by culture; subacute bacterial endocarditis; terminal subarachnoid hemorrhage	No spinal tap, though meningeal syndrome before death was typical	Died; no autopsy
24	M 30	6 months	150/72	Subacute bacterial endocarditis; subacute glomerulonephritis	Uniformly bloody	Died; autopsy: subacute bacterial endocarditis; ruptured mycotic aneurysm; subacute glomerulonephritis
25	F 19	Rheumatic fever at age of 4 years	114/66	Subacute bacterial endocarditis; severe meningeal syndrome	Normal	Died; autopsy: subacute bacterial endocarditis; subacute glomerulonephritis; ruptured mycotic aneurysm

arachnoid bleeding. The spinal canal was not tapped, for fear of augmenting the hemorrhage. Postmortem examination was not made.

The next group (table 4) is that in which clinical and serologic signs of neurosyphilis were shown. Postmortem examination in two cases revealed a ruptured cerebral aneurysm. It is interesting that all four patients with definite cerebrospinal syphilis died; one patient, in addition to this group of three, died suddenly three months after discharge. In another patient with a history of syphilis, serologic tests and the results of neurologic examination were normal. This patient recovered and was well three months after discharge.

The group of cases of blood dyscrasias (table 5) is irregular, and the mortality is evident. In case 30 the spinal fluid was normal, and

at autopsy the subarachnoid hemorrhage, though present, was distinctly less significant than the subdural hemorrhage. In case 31, though no spinal tap was made and no autopsy of the brain was permitted, the clinical picture of a severe meningeal syndrome was typical, though terminal, and a general systemic autopsy showed hemorrhages from every mucous and serous lining in the body.

TABLE 4.—*Data on Patients with Neurosyphilis Who Died on First Admission*

No.	Sex; Age, Yr.	Historical Evidence	Blood Pressure	Clinical Findings	Spinal Fluid	Issue; Anatomic Observations
26	M 37	Chancroids 12 years ago	114/76	Wassermann reaction of blood and spinal fluid 4 plus; curve for cerebrospinal syphilis 4444321100	Uniformly bloody	Died; no autopsy
27	M 27	Chancre 5 years ago	140/80	Wassermann reaction of blood 4 plus	Uniformly bloody	Died; autopsy: syphilitic meningo-encephalitis; ruptured aneurysm at junction of vertebral arteries and basilar artery
28	F 40	Sterility	100/70	Argyll Robertson pupils; Wassermann reaction of blood 2 plus	Uniformly bloody	Died; autopsy: ruptured aneurysm of posterior communicating artery; intraventricular and subarachnoid bleeding

TABLE 5.—*Data on Patients with Blood Dyscrasias Who Died on First Admission*

No.	Sex; Age, Yr.	Historical Evidence	Blood Pressure	Clinical Findings	Spinal Fluid	Issue; Anatomic Observations
29	F 37	History for 6 months; onset of meningeal syndrome after roentgen therapy	114/ 76	Acute myeloid leukemia	Uniformly bloody	Died; no autopsy of brain; acute myeloblastic leukemia with purpuric hemorrhages in all viscera
30	F 50	History of 11 years	230/170	Polycythemia vera	Normal	Died; autopsy: massive subdural hematoma, slight subarachnoid hemorrhage
31	M 15	Epistaxis, 3 months	120/ 75	Thrombocytopenic purpura; undoubted terminal meningeal syndrome	No spinal tap	Died; no autopsy of brain; hemorrhages from every mucous and serous lining in body

The next two cases (table 6) were of men past middle age, with known tuberculosis. The presence of tubercle bacilli in the spinal fluid was not demonstrated. The cause of death was not clear in either case. In spite of all these gaps, we believe there is clinical value in a grouping of cases in this manner.

In the next two cases (table 7) there is suggested rather than demonstrated a relationship of diabetes to subarachnoid hemorrhage

with a rather high mortality. The relationship of diabetes to the cause of death is conjectural.

The last group of patients is of interest (table 8). The ages were 36, 44, 45 and 58, respectively. The blood pressures were low. Two patients were proved at autopsy to have intracranial aneurysm and cerebral arteriosclerosis, even though they were relatively not old. Patient 37, with a proved aneurysm of the posterior communicating

TABLE 6.—*Data on Patients with Known Tuberculosis Who Died on First Admission*

No.	Sex; Age, Yr.	Historical Evidence	Blood Pressure	Clinical Findings	Spinal Fluid	Issue; Anatomic Observations
32	M 56	Known proved tuberculosis 12 years; wife had cough, hemoptysis	146/144	No signs of vascular disease	Xanthochromia; 6 cells; no organism on smear	Died 9 days after admission; no autopsy; cancer (?); tuberculosis (?); vascular disease (?)
33	M 53	Pulmonary tuberculosis 5 years; discharged as having arrested tuberculosis	165/85	Signs in right lung; serologic reaction, smear and culture negative	Uniformly bloody	Died on first admission; no autopsy

TABLE 7.—*Data on Patients with Diabetes Who Died on First Admission*

No.	Sex; Age, Yr.	Historical Evidence	Blood Pressure	Clinical Findings	Spinal Fluid	Issue; Anatomic Observations
34	M 37	None	92/52	Diabetic coma; insulin shock; bronchopneumonia	Blood tinged repeatedly; uniformly bloody	Died on first admission; autopsy: pulmonary tuberculosis and subarachnoid hemorrhage
35	M 31	None	168/95	Urine showed sugar, acetone and albumin	Uniformly bloody	Died; autopsy: aneurysm of anterior cerebral artery with rupture into ventricle, degenerative changes in wall of aneurysm but no signs of arteriosclerosis elsewhere in brain

artery, presented a history of headache, diplopia and ptosis for seven years, a characteristic and anatomically correct symptomatology. None of these patients gave evidence of systemic or vascular disease.

A brief review of the cases in which the immediate mortality was most marked shows that of this group of thirty-nine cases chronic cardiorenal vascular disease was shown in 36 per cent and a clinical course of tumor of the brain in 15 per cent, though in one case the condition proved to be an aneurysm; in 13 per cent the hemorrhage occurred in the course of subacute bacterial endocarditis, and in two groups of 8 per cent each it was associated with cerebrospinal syphilis

and certain blood dyscrasias, respectively. In 5 per cent it was associated clinically with tuberculosis, and in 5 per cent, with diabetes, though in one of these cases there was an aneurysm which may or may not have been related to the diabetes. Last, but not least, there is the group of 10 per cent of the cases in which no clinically discoverable disease was shown; in half of this group aneurysm and cerebral arteriosclerosis were present in relatively young persons.

The group of patients with the next highest gravity of prognosis follows. These patients recovered but are known to have died subsequently. As mentioned previously, they comprise 21 per cent of those

TABLE 8.—*Data on Patients with Intracranial Aneurysm Who Died on First Admission*

No.	Sex; Age, Yr.	Historical Evidence	Blood Pressure	Clinical Findings	Spinal Fluid	Issue; Anatomic Observations
36	F 44	None	120/78	Normal	Uniformly bloody	Died on first admission; autopsy: aneurysm of anterior communicating artery, subarachnoid hemorrhage, cerebral arteriosclerosis
37	F 36	History of headache, diplopia and ptosis 7 years	146/80	Old third nerve paralysis; no vascular disease	Uniformly bloody	Died; autopsy: aneurysm of posterior communicating artery, subarachnoid hemorrhage, cerebral arteriosclerosis
38	F 58	Attack in which could not move legs 3 years ago	100/75	Normal	Uniformly bloody	Died first day; no autopsy
39	F 45	None	88/60	Normal	First examination: 90 red cells; 2d: markedly bloody fluid	Died day of admission; no autopsy

who survived the first admission to the hospital. First to be considered in detail are those with cardiorenal vascular disease (table 9).

The ages of the patients varied from 25 to 58 years, with a median of 48. The blood pressures varied from 150 systolic and 105 diastolic to 190 systolic and 110 diastolic, with a median of 170 systolic and 110 diastolic. Patient 43, though she showed no historical or clinical evidence of vascular or systemic disease, is included because of a diastolic blood pressure of 105. The diagnosis in one case was verified by autopsy. Two patients died suddenly, and one fell and died; we are not certain whether a vascular accident preceded or followed the fall. The time between the initial attack and subsequent death varied from three days to two years.

The percentage of patients with tumor of the brain in this group of persons who died subsequent to the first attack of subarachnoid hemorrhage rises sharply over the percentage of those who died during the

first period of hospital observation (table 10). The incidence is 36 per cent and is 20 per cent of the combined groups of persons who had recurrences and died and those who had previous or subsequent attacks and survived. In the entire group of five cases the tumor was verified anatomically; in two it was a bleeding hemangioma; in two, a spongioblastoma, and in one, a cystic tumor, possibly of gliogenous origin. The patients with spongioblastoma both returned within two months, with definite signs of tumor of the brain. Patient 47, with hemangioma, had

TABLE 9.—*Data on Patients with Cardiorenal Vascular Disease Who Recovered from First Subarachnoid Hemorrhage but Died Subsequently*

No.	Sex; Age, Yr.	Historical Evidence	Blood Pressure	Clinical Findings	Spinal Fluid	Issue; Anatomic Observations
40	F 25	Four attacks of eclampsia	186/130	Chronic glomerulonephritis; hypertension	Turbid; xanthochromia	Died suddenly 3 days after discharge
41	M 58	None	170/110	Generalized arteriosclerosis	Uniformly bloody	Carcinoma of tongue developed 8 mo. later; 9 mo. later, arteriosclerotic ulcer of rectum, then sudden meningeal signs; uniformly bloody spinal fluid; died; autopsy: subarachnoid hemorrhage; chronic productive meningo-encephalitis; no metastases
42	M 51	None	190/110	Sclerosis of radial and temporal arteries	Xanthochromia; crenated red cells	Headaches for 1 year; blood pressure 220/124; 1 year later died
43	F 48	None	150/105	Normal	Uniformly bloody; xanthochromia	2 months later died suddenly
44	M 47	Hypertension 3 years; diabetes 1 year; head injury 3 years ago	170/110	Normal	Uniformly bloody	2 years later patient fell, was injured and died

had a protracted atypical picture when first seen. There was a sciatic syndrome of eight months' duration, with blurred vision. The spinal fluid was xanthochromic but contained no cells. The patient returned two months later, with signs pointing to a tumor of the brain and soon had bloody spinal fluid. Patient 45 had had a convulsion nine years before. Patient 48 had a diagnosis of hemorrhagic meningoencephalitis at the first admission.

The next two cases will be tabulated together (table 11). In case 37, that of syphilis, the characteristic history of pain in the eye and ptosis was presented. The patient died suddenly. In the case of Hodgkin's disease nothing unusual in the course of the subarachnoid hemorrhage was observed.

TABLE 10.—*Data on Patients with Tumor of the Brain Who Survived First Subarachnoid Hemorrhage but Died Subsequently*

No.	Sex; Age, Yr.	Historical Evidence	Blood Pressure	Clinical Findings	Spinal Fluid	Issue; Anatomic Observations
45	M 49	Convulsive seizure 9 years ago; headache 4 months	144/84	Definite signs of brain tumor; frontal calcification shown in roentgenogram	Xanthochromia	Transferred to another hospital; operation: hemangioma; died 4 weeks later
46	M 46	Unconscious 4½ years ago, in bed 2 days; sudden onset of present illness	95/50	Normal	Uniformly bloody	Discharged with diagnosis of ruptured miliary aneurysm; returned 2 months later with papilledema and definite signs of brain tumor; died suddenly; autopsy showed spongioblastoma multiforme
47	F 22	Sciatic syndrome 8 months; blurred vision 2 months	Not taken	Normal	Xanthochromia; no cells	Discharged with diagnosis of sciatic syndrome; returned 2 months later with papilledema and focal signs; xanthochromia of spinal fluid, which was later bloody; operation and autopsy: hemangioma of brain
48	M 47	None	110/70	Normal	Uniformly blood tinged	Discharged with diagnosis of hemorrhagic meningo-encephalitis; 7 years later definite signs of brain tumor, though there was bloody spinal fluid; operation: gliogenous cystic tumor; died 3 months later
49	M 41	Sudden coma 4½ months previously, with rapid recovery; present illness with sudden onset of meningeal syndrome	95/50	Clinical diagnosis rested between ruptured intracranial aneurysm and meningo-encephalitis	Uniformly bloody	Readmitted 6 weeks later with signs pointing to brain tumor; died; autopsy: spongioblastoma multiforme

TABLE 11.—*Data on Patients with Syphilis and Hodgkin's Disease Who Survived First Subarachnoid Hemorrhage but Died Subsequently*

No.	Sex; Age, Yr.	Historical Evidence	Blood Pressure	Clinical Findings	Spinal Fluid	Issue
50	M 36	Chancre 17 years; pain in eye 7 months; ptosis 5 months	140/85	Definite physical signs of cerebrospinal syphilis; Wassermann reaction of blood 4 plus	Uniformly bloody	Died suddenly 3 months later
51	F 13	Present illness 9 months; sudden ictus	114/68	Hodgkin's disease definitely established	Xanthochromia	Died 3 months later

The next two cases (table 12) are those in which there was no sign of clinically discoverable disease. Sudden death overtook both patients, twenty-three months and six months later, respectively. The patients were not old—35 and 48 years, respectively. The blood pressures were low. These cases again suggest the possibility either of

TABLE 12.—*Data on Patients with No Clinically Discoverable Disease Who Survived First Subarachnoid Hemorrhage but Died Subsequently*

No.	Sex; Age, Yr.	Historical Evidence	Blood Pressure	Clinical Findings	Spinal Fluid	Issue; Anatomic Observations
52	M 35	None	116/80	Normal	Xantho-chromia	Did well and worked for 23 months; died suddenly; no autopsy
53	F 48	None	140/80	Normal	Uniformly bloody	Suddenly dropped dead in the street 6 months later; no autopsy

TABLE 13.—*Data on Patients with Cardiorenal Vascular Disease Who Survived First Subarachnoid Hemorrhage but Were Not Followed*

No.	Sex; Age, Yr.	Historical Evidence	Blood Pressure	Clinical Findings	Spinal Fluid
54	F 47	Occasional neuralgic pain in one eye for 7 years	130/ 70	Moderate sclerosis of retinal vessels	Xanthochromia
55	M 43	Hypertension and coronary disease 10 years	180/104	Essential hypertension; coronary disease; hypertensive retinitis	Uniformly bloody
56	F 50	Hypertension 10 years	196/112	Cerebral arterio-sclerosis	130 red cells; uniformly bloody
57	F 58	Hypertension 6 years	190/100	Generalized and cerebral arteriosclerosis	Uniformly bloody
58	M 64	Chronic alcoholism; epigastric symptoms 1½ years; recent mental changes	200/100	Generalized arterio-sclerosis; peripheral alcoholic neuritis; chronic alcoholism (liver); pachymeningitis haemorrhagica interna	420 red cells; xanthochromia
59	M 48	None	110/ 70	Sclerotic changes in retinal vessels	Uniformly blood tinged; 33 white cells

congenital aneurysm or of aneurysm with cerebral arteriosclerosis in relatively young persons. Postmortem examinations were not made.

The next general group of patients are those who recovered but were not followed after discharge, either because trace of them was lost or because the cases were too recent. The cases have less clinical value because the outcome is not known. Nevertheless, they deserve mention and are useful for comparison.

Six patients showed evidence of cardiorenal vascular disease (table 13). The ages varied from 43 to 64 years, with a median of 49 years.

The blood pressures varied from 110 systolic and 70 diastolic to 200 systolic and 100 diastolic, with a median of 185 systolic and 100 diastolic.

The next five cases are nondescript, with a variable outlook, and are tabulated together (table 14).

TABLE 14.—*Data on Patients with Various Diseases Who Survived First Subarachnoid Hemorrhage but Were Not Followed*

No.	Sex; Age, Yr.	Historical Evidence	Blood Pressure	Clinical Findings	Spinal Fluid
60	M 57	Tuberculosis at age of 28; influenza at 50; pneumonia at 56	140/ 75	Normal	Xanthochromia; 5 white cells
61	M 43	Epilepsy since age of 16; chronic alcoholism	120/ 80	Normal	Uniformly bloody
62	M 30	Epileptiform fainting spells until age of 14	115/ 70	Normal	Uniformly bloody; xanthochromia
63	M 36	Typical history of acute infection and acute glomerulonephritis	190/100; subsequently back to normal	Acute glomerulonephritis; urine: faint trace albumin, specific gravity 1.010; 10-15 white cells; 1-2 red cells	Uniformly bloody; xanthochromia
64	F 19	Cardiac disease 3 years	Not recorded	Sign of subacute bacterial endocarditis; positive blood culture; Streptococcus viridans	Uniformly bloody

TABLE 15.—*Data on Patients with No Discoverable Disease Who Were Not Followed After Recovery from Subarachnoid Hemorrhage*

No.	Sex; Age, Yr.	Historical Evidence	Blood Pressure	Clinical Findings	Spinal Fluid
65	M 51	None	150/78	Normal	Uniformly bloody
66	F 33	None	108/65	Korsakoff mental changes; encephalogram shows symmetrical internal hydrocephalus due to communicating hydrocephalus	Uniformly bloody; xanthochromia
67	M 40	None	110/50	Normal	Uniformly blood tinged
68	M 32	Onset during exertion	118/60	Normal	Xanthochromia; 185 lymphocytes

In the last group of four cases there was no clinical evidence of discoverable disease, and the number comprise 27 per cent of the group to which it belongs (table 15). The ages were 32, 33, 40 and 51 years, respectively. The blood pressures varied from 108 systolic and 65 diastolic to 150 systolic and 78 diastolic.

The next group consists of patients who improved and were followed for less than one year. The first special group (table 16)

are those with obvious cardiorenal vascular disease. The ages varied from 32 to 56, with a median of 53. The blood pressures varied from 114 systolic and 80 diastolic to 280 systolic and 140 diastolic, with a median of 180 systolic and 110 diastolic.

TABLE 16.—*Data on Patients with Cardiorenal Vascular Disease Who Improved After Subarachnoid Hemorrhage and Were Followed Less Than One Year*

No.	Sex; Age, Yr.	Historical Evidence	Blood Pressure	Clinical Findings	Spinal Fluid	Issue; Anatomic Observations
69	F 32	4 years ago attack of dyspnea; palpitation, headache for 3 months	230/135	Peripheral sclerosis; binasal hemianopia; arterial hypertension	Uniformly bloody	Followed 10 months; Bell's palsy; otherwise well
70	M 56	None	114/ 80	Retinal and peripheral arterio-sclerosis	Uniformly bloody	Followed 6 months; persistent headaches; unable to work
71	F 53	Hypertension and heart failure for 5 years	280/140	Hypertension; heart disease; auricular fibrillation	Uniformly bloody	Followed 5 months; subjectively slight improvement
72	F 52	None	180/110	Normal	Uniformly bloody	Followed 7 months; doing well; blood pressure 188/118
73	F 56	Severe frontal headache twice weekly for 1 year	168/ 80	Peripheral sclerosis	Uniformly bloody	Followed 4 months; frequent mild headache and stiff neck

TABLE 17.—*Data on Patients with Suspected Tumor of the Brain Who Improved After Subarachnoid Hemorrhage but Were Followed Less Than One Year*

No.	Sex; Age, Yr.	Historical Evidence	Blood Pressure	Clinical Findings	Spinal Fluid	Issue; Anatomic Observations
74	F 23	None	100/68	Papilledema; hemi-chromatonopia brain tumor suspected	680 red cells; xantho-chromia	Followed 6 months; still had symptoms; no papilledema
75	M 27	None	126/88	Transitory focal signs; tumor of left temporal lobe suspected	Red cells; white cells; xantho-chromia; large, peculiar cells suspected to be tumor cells	Followed 9 months; feeling fairly well; spinal fluid normal; patient discharged for further observation

Two patients suspected of having tumor of the brain are included in the group shown in table 17. Both are being observed at short intervals. No final conclusion can be vouchsafed about either.

One patient had a history of gonorrhea and syphilis (table 18). There were palpable epitrochlear and inguinal glands, but serologic tests and the physical examination were without significance.

The next group of cases (table 19) is that in which there were no signs of local, systemic or vascular disease. The ages varied from 15 to 57, with a median of 34 years. The blood pressures varied from 112 systolic and 54 diastolic to 145 systolic and 80 diastolic with a median of 134 systolic and 80 diastolic. This group of five patients

TABLE 18.—*Data on Patient with Evidence of Syphilis and Gonorrhea Who Improved After Subarachnoid Hemorrhage but Was Followed Less Than One Year*

No.	Sex; Age, Yr.	Historical Evidence	Blood Pressure	Clinical Findings	Spinal Fluid	Issue; Anatomic Observations
76	M 25	Gonorrhea 3 years ago; syphilis 2½ years ago; headaches for 12 years	110/80	Palpable epitrochlear and inguinal glands; serologic and physical findings negative for syphilis	Uniformly bloody; xanthochromia	Followed for 3 months; feeling well

TABLE 19.—*Data on Patients with No Evidence of Disease Who Recovered from Hemorrhage but Were Followed Less Than One Year*

No.	Sex; Age, Yr.	Historical Evidence	Blood Pressure	Clinical Findings	Spinal Fluid	Issue; Anatomic Observations
77	F 15	None	112/54	Normal; Korsakoff mental picture	Uniformly bloody	Followed 7 months; doing well
78	F 34	None	145/80	Normal; lymphhemangioma of buttock; calcification in the falx	Uniformly bloody	Followed 10 months; occasional headache
79	F 25	None	134/80	Normal	Uniformly bloody	Followed 9 months; feels fine, working
80	F 50	None; convalescing from bronchopneumonia	140/80	Normal	Uniformly bloody	Followed 1 month; feeling well
81	M 57	None; discharge from left ear 30 years ago, with flareup 4 months ago; appendectomy 6 weeks ago; spinal anesthesia	128/94	Normal	160/236 red cells; xanthochromia	Followed 1 month; aphasia and mental symptoms developed; patient then lost trace of

comprises 38 per cent of the number who recovered and were followed for less than one year.

The next group are the patients who improved, had no recurrence and were followed for from one to over eight years. They fall into two almost equal groups: those with vascular disease and those with no clinically discoverable disease. The patients with the more rapidly fatal diseases have disappeared from this group in which there was long time observation.

The first group showed clinical evidence of vascular disease (table 20). The ages varied from 40 to 68 years, with a median age of 55.

The blood pressures varied from 290 systolic and 170 diastolic to 110 systolic and 88 diastolic, with a median of 178 systolic and 90 diastolic.

The group of patients with no clinically discoverable disease is next presented and consists of 46 per cent of the group with this expectancy (table 21). The ages varied from 18 to 54 years, with a median of 33 years. The blood pressures varied from 110 systolic and 70 diastolic to 148 systolic and 100 diastolic, with a median of 130 systolic and 90 diastolic.

At this point we consider the most interesting group of the entire series: patients who suffered previous or subsequent attacks of sub-

TABLE 20.—*Data on Patients with Vascular Disease Who Had No Recurrence of Hemorrhage and Were Followed More Than One Year*

No.	Sex; Age, Yr.	Historical Evidence	Blood Pressure	Clinical Findings	Spinal Fluid	Period Followed, Yr.	Issue
82	F 54	None	180/ 95	Arteriosclerotic retina	Uniformly bloody	5	Symptoms only of coronary disease
83	M 40	Moderately alcoholic	170/ 86	Generalized arteriosclerosis	Uniformly bloody	4	Working; feels well
84	F 58	None	110/ 88	Korsakoff mental picture; ventriculogram showed symmetrical internal hydrocephalus	Uniformly bloody; xanthochromia	4	Occasional headaches
85	F 40	Hypertension 9 years	290/170	Essential hypertension; arteriosclerosis; albuminuric retinitis	Uniformly bloody	3	Readmitted for hemorrhage into eye and heart disease
86	M 55	Cardiac history 16 years	178/100	Generalized arteriosclerosis; coronary disease	Xanthochromia	2	Signs of coronary disease; blood pressure 165/100
87	M 55	Intermittent headache for 5 years	150/ 80	Slight thickening of peripheral vessels	Uniformly bloody	2	"Feeling fine" was communication from patient
88	F 68	Mental changes 1 year	180/ 90	Arteries of fundus thin, but not markedly	Uniformly bloody; xanthochromia	1	Mental changes; readmitted for carcinoma of rectum

arachnoid hemorrhage, either proved or presumptive (table 22). There is a total of eleven patients—two with both previous and subsequent proved attacks who were followed for from one to three years after the last attack and were fairly well, one with a previous proved attack who has been followed after his last attack and three without previous attacks but with proved subsequent attacks. Two patients had presumptive previous attacks during which no spinal tap was done, and one patient, a presumptive previous attack during which spinal tap showed clear fluid and from 11 to 19 lymphocytes. Two patients had presumptive subsequent attacks, both with definite meningeal syndromes and normal spinal fluid, in one of whom there developed paralysis of the left third nerve, which persisted for at least three months.

The patients in this group presented several characteristic features. They were relatively young, their ages varying from 14 to 60 years, with a median of 28 years. The blood pressures were low, varying from 80 systolic and 50 diastolic to 160 systolic and 94 diastolic, with a median of 125 systolic and 80 diastolic. Only the two oldest patients in the group of eleven, or 18 per cent, showed any evidence of systemic or vascular disease. The others showed no signs of clinically discoverable disease. Eighty-two per cent of the patients were in this group, certainly a significant number. It is in cases of this sort that one expects

TABLE 21.—*Data on Patients with No Discoverable Disease Who Had No Recurrence of Hemorrhage and Were Followed More Than One Year*

No.	Sex; Age, Yr.	Historical Evidence	Blood Pressure	Clinical Findings	Spinal Fluid	Period Followed, Yr.	Issue
89	F 50	Headaches since childhood on left side	130/ 90	Normal; no changes of vessels in fundi though hemorrhages on admission	Uniformly bloody	8	Feels well; operated on for ovarian cyst
90	F 18	None	110/ 70	Normal	Uniformly bloody	4	Feels well; residual signs
91	M 54	None	120/ 64	Normal; no peripheral sclerosis; slight denting of veins in fundus, though vessels appear normal	Uniformly bloody	2	Works but feels weak
92	M 33	Normal except for acute attack of renal disease 11 years ago	135/ 92	Normal; hemorrhage in fundi; no sclerosis of vessels	Uniformly bloody	1	Comfortable; residual signs
93	M 22	Alcoholic 4 years	.....	Normal; question of possible toxic encephalitis or pachymeningitis haemorrhagica interna	Uniformly bloody	1	Feels well
94	M 39	Sudden onset during coitus	148/100	Normal	Uniformly bloody	1	No signs or symptoms

to find congenital aneurysm or early cerebral arteriosclerosis, if autopsy is performed.

Concerning the patients with presumptive attacks, it has been established that subarachnoid hemorrhage can occur and not be evident in the spinal fluid on lumbar puncture. It has been postulated and proved that an adhesive process may develop about a slowly leaking aneurysm. Patient 103 entered the hospital with a definite meningeal syndrome, and a diagnosis of subarachnoid hemorrhage was made, on the basis of a ruptured arteriosclerotic aneurysm. Lumbar puncture showed no blood, but the clinical diagnosis of arteriosclerotic aneurysm was not changed by the staff. The patient returned to the hospital three months later, with a second meningeal syndrome and uniformly

TABLE 22.—*Data on Patients with Previous or Subsequent Attacks of Subarachnoid Hemorrhage*

No.	Sex; Age, Yr.	Previous Attacks	Blood Pressure	Clinical Findings	Spinal Fluid	Subsequent Attacks	Issue
95	F 28	Proved attack 16 years ago; recurrence every 2-3 years; transitory hypertension 5th month of pregnancy; present illness 3 weeks before delivery	120/70	Normal	Uniformly bloody	One attack 6 months later	Followed 3 years after last attack; feels well
96	M 38	Proved attack 16 years ago	125/75	Normal	Uniformly bloody	One attack 6 years later	Followed 15 months later; persistent mental changes
97	M 21	Proved attack 4 years ago	136/84	Normal	Bloody	None	Followed 1 year; feels well
98	M 35	None	135/85	Normal	Bloody	One proved attack 3 weeks later	Recovered; not followed
99	M 14	None	125/95	Normal	Xanthochromia; 290 red cells	Proved recurrence 17 months later	In hospital
100	F 60	None	160/94	Peripheral arteriosclerosis	Uniformly bloody	Recurrence with hemiplegia 9 months later	Improved; not followed
101	F 23	Sudden meningeal syndrome 8 years ago; no spinal tap; diagnosis of encephalitis	130/80	Normal	Bloody	None	Followed 6 months; well; shows enlarged blindspot
102	M 24	Sudden stiff neck, headaches and mild fever 5 years ago; transient confusion; two recurrences in intervening 5 years	80/50	Normal	Uniformly bloody; Wassermann reaction negative; colloidal gold curve 5555553100	Improved	Not followed
103	F 53	Sudden meningeal syndrome 3 months ago; normal spinal fluid; 11-19 lymphocytes	144/88	Retinal arteriosclerosis	Uniformly bloody	None	Followed 4 months; persistent headache
104	F 34	None	106/68	Normal	Uniformly bloody	Meningeal syndrome 3 months later; normal spinal fluid	Recovered; not followed
105	M 17	None	105/65	Normal	Uniformly bloody	Sudden recurrence of meningeal syndrome, with left third nerve paralysis 5 weeks later; spinal fluid clear; 8 lymphocytes	Followed for 3 months; no symptoms; signs persist

bloody spinal fluid. Case 104 is the converse of case 103. This young woman recovered from a typical subarachnoid hemorrhage and returned three months later with a similar meningeal syndrome, but the spinal fluid was normal. We are forced to the conclusion that the meningeal syndromes associated with normal spinal fluid represent either slow leaks which are sealed off promptly close to the aneurysm or dissection of the wall of the aneurysm with a mild meningeal inflammatory process about it, giving symptoms. Case 105 is an example of a similar condition. A boy aged 17 recovered from a typical subarachnoid hemorrhage. Five weeks later he was taken suddenly with a severe meningeal syndrome and paralysis of the left third nerve. The spinal fluid was clear and colorless and showed 8 lymphocytes per cubic millimeter. The significance of paralysis of the third nerve in relation to aneurysm of the posterior communicating artery has already been touched on. At this point, it is of interest to recall case 37, that of a woman aged 36 who had a history of headache, diplopia and ptosis for seven years. She died of a subarachnoid hemorrhage, and autopsy showed an aneurysm of the posterior communicating artery and cerebral arteriosclerosis.

Instances of presumptive previous attacks are cases 101 and 102. Case 101 was that of a woman who at the age of 15 years had suffered a sudden, severe meningeal syndrome and had recovered. No tap was made, and the condition was diagnosed as encephalitis. Eight years later a typical subarachnoid hemorrhage took place, with bloody spinal fluid. In case 102 the evidence is more convincing. A youth, at the age of 19, suffered a sudden, severe meningeal syndrome, with mild fever and transient confusion. No spinal tap was made. In the next five years there were two recurrences, during which no spinal tap was made. At the age of 24, during his fourth attack, the patient was admitted to the hospital. The spinal fluid was uniformly bloody. Serologic tests gave negative results. There was nothing to suggest congenital or acquired syphilis. The colloidal gold curve was 5555553100.

Although in the last two cases the diagnosis was not proved, there were certainly presumptive previous attacks. Our experience in these cases has led us to inquire carefully of all patients with subarachnoid hemorrhage for previous episodes of meningeal involvement, and we believe that we are justified clinically in assuming that these attacks represent subarachnoid bleeding.

A consideration of the cases on the basis of the underlying disease is the next important method of examining the series. No time need be spent on diseases such as tumor of the brain, subacute bacterial endocarditis and blood dyscrasias. The subarachnoid hemorrhage is purely symptomatic and is sometimes terminal. The relationship of tuberculosis and diabetes is not clear in the cases in our series. The cases of symptomatic epilepsy or epileptiform attacks prove no point, since the

patients recovered and were not followed. In the one case in which the hemorrhage occurred during acute glomerulonephritis the patient was not followed.

The patients with clinically definite cerebrospinal syphilis died, three during the first attack and one shortly and suddenly thereafter. Two of the patients showed ruptured cerebral aneurysm.

What really concerns one here is a comparison of the patients with cardiovascular disease and those with no clinically discoverable systemic disease. The two groups together comprise sixty-nine patients, or 65 per cent of the entire series.

The material will be slightly rearranged in the comparison of patients with cardiorenal vascular disease and those without discoverable disease.

	Died on First Admission	Died Subsequently	Recovered, Not Followed	Followed 1 Year	Followed from 1 to 8 Years	Recurrence, but Recovery
Cardiovascular disease	14	5	6	5	7	2
No disease	4	2	4	5	6	9
Total number of patients	18	7	10	10	13	11

When one considers the incidence for the two general groups only, the patients with vascular disease and those with no disease, for each particular mortality and prognosis, the ratios, expressed in percentages, are as follows:

	Died on First Admission	Died Subsequently	Recovered, Not Followed	Followed 1 Year	Followed from 1 to 8 Years	Recurrence, but Recovery
Cardiovascular disease, %	78	72	60	50	54	18
No disease, %	22	28	40	50	46	82
Total number of patients	18	7	10	10	13	11

As the clinical course lengthens and apparently becomes more benign the definite increase in the percentage of patients with no discoverable disease is striking and gives at this point the most important index of prognosis. This, together with the peculiarities of history which we have noted in the group of recovered patients who survived recurrences, gives another important favorable prognostic index.

When one considers in another way the group of patients with cardiovascular disease as compared with the group with no disease, according to percentages within the disease group for mortality and prognosis, the following figures appear:

	Cardiovascular Disease, Percentage	No Clinically Discoverable Disease, Percentage
Died at first admission	36	13
Died subsequently	13	7
Improved; not followed	15	13
Followed 1 year	13	17
Followed from 1 to 8 years	18	20
Recurrences but recovered	5	30
	100 (39 cases)	100 (30 cases)

The general trend of the group with cardiovascular disease to fall into the earlier brackets, with the greatest mortality, and for the group with no disease to fall into the lower brackets, with the more favorable outlook, is obvious.

A comparison for median age groups is also presented.

	Cardiovascular Disease		No Disease	
	Age in Years	Number of Patients	Age in Years	Number of Patients
Died on first admission	50	14	36; 44; 45; 58	4
Died subsequently	48	5	35; 48	2
Improved; not followed	49	6	32; 33; 40; 51	4
Followed 1 year	53	5	34	5
Followed from 1 to 8 years	55	7	33	6
Recurrence but recovered	53; 60	2	24	9

Within the group of patients showing cardiovascular disease there is no correlation between age and outlook. There is a distinct difference in age between the entire group with cardiovascular disease and the group with no disease, and within the group with no disease there is a definite tendency for the patients to become younger as they approach the more favorable brackets.

CONCLUSIONS AND SUMMARY

1. Spontaneous subarachnoid hemorrhage bears the prognosis of the underlying disease.

2. Spontaneous subarachnoid hemorrhage may be symptomatic of cardiorenal vascular disease, tumor of the brain, subacute bacterial endocarditis, purpura, polycythemia, Hodgkin's disease or myeloid leukemia. It may be associated with cerebrospinal syphilis, tuberculosis, diabetes, epilepsy or acute glomerulonephritis, or there may be no clinically discoverable disease.

3. In the only four cases in which the hemorrhage was associated with clinically definite cerebrospinal syphilis, the patients died.

4. The prognosis tends to be worse with the presence of generalized vascular disease and better in the absence of clinically discoverable disease.

5. In the absence of discoverable disease the prognosis becomes worse the older the patient.

6. In the absence of generalized disease, a history of proved or presumptive previous attacks tends to make the prognosis better. This history is usually found in young persons and suggests congenital aneurysm or aneurysm with cerebral arteriosclerosis in young persons.

7. The average duration between the observed attack and the next expected attack is two years and six months.

8. Presumptive recurrences occur, even though not proved by examination of the spinal fluid.

EPILEPTIFORM CONVULSIONS FROM "REMOTE" EXCITATION

FREDERICK A. FENDER, M.D.*
SAN FRANCISCO

By the use of a method worked out by Dr. W. J. Merle Scott, of the University of Rochester School of Medicine, and me permitting stimulation of the nervous system of an intact and unanesthetized animal, epileptiform seizures have been produced that seem somewhat more complete than those usually reported as having followed electrical stimulation. A full description of the stimulating mechanism will be included in the reprints of this article. It may suffice to say here that, like the method of Light and Chaffee,[1] it involves the use of a secondary coil embedded in the tissues which is excited, after operation, when the subject is placed in a fluctuating electromagnetic field. I shall report our experiments briefly and make a few comments on the literature of the subject.

It must have been gratifying to Broca [2] and Bastian,[3] and particularly to Hughlings Jackson,[4] who had been preaching cerebral localization to an unresponsive medical profession, to hear of the experiments of Fritsch and Hitzig.[5] The last two investigators, forsaking the dogma of the day for further experimental work, first showed that electrical stimulation of the "motor area" of the cerebral cortex evoked consistent responses from contralateral muscles. Of less importance, but pertinent

---

*Fellow of the Rockefeller Foundation.

From the Department of Surgery, the Stanford University School of Medicine.

Financed by grants from the Committee on Scientific Research of the American Medical Association.

1. Light, Richard U., and Chaffee, E. L.: Electrical Excitation of the Nervous System—Introducing a New Principle: Remote Control; Preliminary Report, Science **79**:299 (March 30) 1934. Chaffee, E. Leon, and Light, Richard U.: A Method for the Remote Control of Electrical Stimulation of the Nervous System, Yale J. Biol. & Med. **7**:83 (Dec.) 1934.

2. Broca, Paul: Remarques sur le siége de la faculté du langage articulé suivies d'une observation d'aphémie, Bull. Soc. anat. de Paris **36**:330, 1861; Nouvelle observation d'aphémie produite par une lésion de la moitié postérieure des deuxième et troisième circonvolutions frontales, ibid. **36**:398, 1861.

3. Bastian, H. Charlton: Note on the Localization of Function in the Cerebral Hemispheres, J. Ment. Sc. **14**:454, 1869.

4. Jackson, J. Hughlings: Illustrations of Diseases of the Nervous System, Clin. Lect. & Rep. London Hosp. **1**:337, 1864; Loss of Speech, ibid. **1**:388, 1864.

5. Fritsch, G., and Hitzig, E.: Ueber die electrische Erregbarkeit des Grosshirns, Arch. f. Anat., Physiol. u. wissensch. Med., 1870, p. 300.

to this paper, were the secondary findings that prolonged stimulation produced focal convulsive movements and that generalized epileptiform convulsions, characterized by "tonic" and "clonic" contractions, might follow when stimulation was continued still longer.

Ferrier, beginning his work shortly afterward, amplified and extended the experiments.[6] He described both focal and general convulsions following faradization of the cortex, and evoked seizures by stimulation of portions of the cortex other than the motor area, though not with the same facility. This finding subsequently was more firmly established by Munk.[7] Ferrier obtained the convulsions in the rabbit, cat, dog and monkey. His work established an important correlation with the clinical observations of Hughlings Jackson[8]: When a generalized convulsion follows stimulation of the motor cortex, the convulsion begins in the muscles primarily set in action and proceeds by a definite "march" to involve other parts of the body. The "discharge" theory of the production of the epileptic seizure apparently was vindicated.

In 1876 François-Franck and Pitres[9] undertook a thorough study of the responses of the cerebral cortices of animals to electrical stimulation. Besides study of the effects produced by stimulation after a variety of anatomic alterations, perhaps their chief contribution was the graphic analysis of the muscular contractions (frequency, delay, fusion and summation) produced, though in one important respect this work has been shown to have been in error. Their conclusions following failure to produce "complete convulsions" by stimulation of subcortical levels have stood until recently. This matter will be referred to later.

The new field of investigation inevitably attracted a number of investigators during the next few years. In addition to reports already cited, the work of the following investigators should be mentioned as bearing

---

6. Ferrier, David: Experimental Researches in Cerebral Physiology and Pathology, West Riding Lun. Asyl. Rep. **3**:30, 1873; The Functions of the Brain, London, Smith, Elder & Co., 1876.

7. Munk, Hermann: Ueber die Functionen der Grosshirnrinde, Berlin, A. Hirschwald, 1881.

8. Jackson, J. Hughlings: On the Anatomical and Physiological Localization of Movements in the Brain, Lancet **1**:84, 162 and 232, 1873.

9. François-Franck, and Pitres, A.: Recherches expérimentales et critiques sur les convulsions épileptiformes d'origine corticale, Arch. de physiol. norm. et path. **2**:1 and 101, 1883; Recherches expérimentales et critiques sur l'excitabilité des hémisphères cérébraux, ibid. **5**:7 and 149, 1885. François-Franck: Leçons sur les fonctions motrices du cerveau, Paris, Octave Doin, 1887.

on the electrical production of convulsions: Bubnoff and Heidenhain,[10] Beevor and Horsley,[11] Gotch and Horsley,[12] Grünbaum and Sherrington,[13] Broca and Richet,[14] Horsley and Schäfer[15] and Rothman,[16] as well as, later, the extensive studies of the Vogts.[17]

Within four years of the discovery of electrical excitability of the cerebrum in animals, Bartholow[18] stimulated the cortex of Mary Rafferty, aged 30, a domestic, whose brain had been exposed through the ravages of an epithelioma, produced by a bit of whalebone in her wig. In one observation, the patient being conscious, the "right posterior lobe" was faradized.

> Very soon the left hand was extended as if in the act of taking hold of some object in front of her; the arm presently was agitated with clonic spasms; her eyes became fixed, with pupils widely dilated; lips were blue, and she frothed at the mouth; her breathing became stertorous; she lost consciousness, and was violently convulsed on the left side. The convulsion lasted five minutes and was succeeded by coma.

By 1890 stimulation of the human cerebral cortex, frequently with an epileptiform convulsion as a sequel, had been carried out by Scia-

---

10. Bubnoff, N., and Heidenhain, R.: Ueber Erregungs- und Hemmungsvorgänge innerhalb der motorischen Hirncentren, Arch. f. d. ges. Physiol. **26**:137, 1881.

11. Beevor, Charles E., and Horsley, Victor: An Experimental Investigation into the Arrangement of the Excitable Fibres of the Internal Capsule of the Bonnet Monkey, Phil. Tr. (B) **181**:49, 1890; A Record of the Results Obtained by Electrical Excitation of the So-Called Motor Cortex and Internal Capsule in an Orang-Outang, ibid. **181**:129, 1890.

12. Gotch, Francis, and Horsley, Victor: On the Mammalian Nervous System, Its Functions, and Their Localization Determined by an Electrical Method, Phil. Tr. (B) **182**:267, 1891.

13. Grünbaum, A. S. F., and Sherrington, C. S.: Observations on the Physiology of the Cerebral Cortex of Some of the Higher Apes, Proc. Roy. Soc., London **69**:206, 1901.

14. Broca, André, and Richet, Charles: Période réfractaire dans les centres nerveux, Compt. rend. Acad. d. sc. **124**:96, 1897; Période réfractaire dans les centres nerveux, ondulation nerveuse, et conséquences qui resultent au point de vue de la dynamique cérébrale, ibid. **124**:573, 1897; Période réfractaire et synchronisation des oscillations nerveuses, ibid. **124**:697, 1897.

15. Horsley, Victor, and Schäfer, E. A.: Experiments on the Character of Muscular Contractions Which Are Evoked by Excitation of the Various Parts of the Motor Tract, J. Physiol. **7**:96, 1886.

16. Rothman, Max: Die Erregbarkeit der Extremitätregion der Hirnrinde nach Ausschaltung cerebrospinaler Bahnen, Ztschr. f. klin. Med. **44**:183, 1902.

17. Vogt, Cécile, and Vogt, O.: Zur Kenntnis der elektrisch erregbaren Hirnrinden-Gebiete bei den Säugetieren, J. f. Psychol. u. Neurol. **8**:277, 1907.

18. Bartholow, Roberts: Experimental Investigations into the Functions of the Human Brain, Am. J. M. Sc. **67**:305, 1874.

manna,[19] Horsley,[20] Keen,[21] Nancrede,[22] Lloyd and Deaver,[23] Mills[24] and Beevor and Horsley.[11] In 1897 Lamacq[25] collected the observations of a number of surgeons, and during the present century electrical stimulation of the human cerebral cortex, often accompanied by focal convulsive attacks, has become almost a surgical commonplace.

To summarize: The production of epileptiform convulsions by electrical stimulation of the cerebral cortex has been amply demonstrated in a variety of mammals, including man. The results of subcortical stimulation will be touched on after protocols of experiments in which our method was used in the unanesthetized dog.

EXPERIMENTAL WORK

By "stimulation" in the following notes I refer to stimulation with an alternating current with a frequency of 60 cycles following a sine wave. The current used cannot be estimated accurately, but it probably always was less than 3 milliamperes. It should be stated here that in no case did an animal show evidence of pain. Willingness to submit to subsequent stimulation seems to indicate that no unpleasant sensation was experienced.

EXPERIMENT 1.—A female fox terrier, weighing 10 Kg., was prepared, under ether anesthesia.

Operation.—With a testing primary coil in place at the operating table, the brain was exposed through a right temporal incision. The motor cortex was identified, and the hindleg area of the posterior sigmoid gyrus was chosen for the placing of the active electrode of the stimulating element. In the sulcus between the anterior and the posterior sigmoid gyrus was an artery. However, direct stimulation of the artery was not followed by visible constriction or blanching of the distal areas. The electrode was placed at a distance of from 2 to 3 mm. and anchored in place by one suture of fine, braided silk, passed through the overlying dura. The indifferent electrode, a small silver plate, was slipped under the

19. Sciamanna, E.: Gli avversari delle localizzazioni cerebrali, Arch. di psichiat. **3**:209, 1882; quoted by Lamacq.[25]

20. Horsley, Victor: Case of Occipital Encephalocele in Which a Correct Diagnosis Was Obtained by Means of the Induced Current, Brain **7**:228, 1884.

21. Keen, W. W.: Three Successful Cases of Cerebral Surgery, Am. J. M. Sc. **96**:452, 1888.

22. Nancrede, Charles B.: Two Successful Cases of Brain Surgery, M. News **53**:584 (Nov. 24) 1888.

23. Lloyd, James Hendrie, and Deaver, John B.: A Case of Focal Epilepsy Successfully Treated by Trephining and Excision of the Motor Centres, Am. J. M. Sc. **96**:477, 1888.

24. Mills, Charles K.: Cerebral Localization in Its Practical Relations, Brain **12**:233, 1889-1890.

25. Lamacq, Lucien: Les centres moteurs corticaux du cerveau humain, Arch. clin. de Bordeaux **6**:491, 1897.

temporal muscle. The wound was closed in four layers with interrupted sutures of fine silk. Momentary stimulation at the end of operation evoked a prompt tetanic response, the left hindleg only participating.

Stimulation.—The animal made a prompt recovery, taking food and behaving normally from the first postoperative day. On this day a test stimulation of one second gave a tetanic contraction of the left hindleg only. No weakness was seen of either leg on the left.

On the third postoperative day, no neurologic sequels to the operation having appeared, stimulation was carried out for ten seconds. The usual tetanic contraction of the left hindleg was produced. The animal was released and ran actively about the room. After approximately ten seconds, spasmodic contractions of the left hindleg occurred, which interfered with locomotion. These were convulsive and sudden and appeared to be chiefly those of flexion, whereas extension had predominated during stimulation. After approximately thirty seconds, the subject slumped to the floor and began, gradually, to have more violent contractions on the left side. The left hindleg was first affected; next, the muscles of the trunk on the left side, and, finally, the left foreleg, neck and face, in what appeared to be a typical "march." Clonus began at the rate of 2 or 3 a second, the interval increasing as the attack wore on. With spread to the entire left side, all muscles affected contracted in unison. There were "frothing" and biting movements of the jaws. The neck was bent sharply to the left during the latter part of the attack, which lasted from two to three minutes and wore off gradually. As the interval between contractions lengthened, the animal attempted to stand but could not, for perhaps a minute or more. Within five minutes from the onset of the attack, standing was possible. The difficulty on first attempts appeared to be in weakness of the left legs, the animal consistently falling to the left. Shortly after regaining the ability to stand, the animal was able to run about the room in a normal manner. Evidence of weakness on the left had disappeared.

EXPERIMENT 2.—A female wire-haired fox terrier, weighing 6.5 Kg., was used.

Operation.—Exposure and anesthesia were produced as in experiment 1, and the motor cortex was identified, with the use of an inductorium so adjusted that a weak contraction of the temporal muscle was evoked. As in the first case, an artery coursed between the anterior and the posterior sigmoid gyrus. Direct stimulation of this vessel with the inductorium (bipolar leads 2 mm. apart) failed to produce any noticeable constriction or blanching, and stimulation of the minute pial vessels of the region likewise failed to evoke visible change. The bared end of the silver wire serving as the active electrode was implanted in the hindleg area. When a testing primary coil was brought into position, a tonic contraction limited to the left hindleg was produced. Closure was made as before.

Stimulation.—Two days after operation the animal was in good condition and behaved normally. No weakness of the left legs was in evidence. Stimulation was carried out for twenty-five seconds. During the first ten seconds the usual tonic contraction of the left hindleg was seen, without attempts at evasion or evidence of discomfort. Toward the end of this period, gradually, the motions of this extremity began to be characterized by alternate flexion and extension, at a rhythm of about 2 a second. Stimulation was continued for fifteen seconds, and the animal was placed on the floor, at liberty. Ten seconds later, the motions of the hindleg having continued steadily at the same rate of intensity and at the same frequency, the "march" was seen to begin. The left foreleg, the muscles of the left side of the trunk and, finally, the muscles of the neck and face on the left side were seen to be in clonic convulsion synchronously and at the rate of about 2 a second. There

followed biting and opening motions of the jaws, at the same rhythm, and then, almost at one time, involvement of the entire right side. This extension took place so rapidly that we were unable to make out the sequence of events. Drooling and frothing appeared at this time. The general attitude of the neck and trunk was that of flexion toward the left. The left eye was deviated toward the left during the height of the attack but returned to the midline after a few seconds. Motions of the eyes were difficult to observe.

Contractions moderated in violence and decreased in frequency after three and one-half minutes. At the end of five minutes they had ceased, and the subject lay quietly, apparently unconscious. Between this time and the end of another minute, sudden noise (a handclap) produced momentary violent extension of all legs. Shortly after the end of six minutes the animal was conscious, and standing was possible. At the end of ten minutes she was able to walk about the room. For the next thirty minutes there was weakness of the left legs, chiefly the hindleg, the foot of this leg turning under in walking and giving way while standing. The weakness wore off gradually during the half-hour following the termination of the attack.

EXPERIMENT 3.—A female bulldog, weighing 19 Kg., was used.

Operation (9: 30 a. m.).—The same operative technic was used as before. The neck area of the motor cortex was selected for implantation of the active electrode. As in the last experiment, the vessels of the region, including the artery mentioned, were stimulated by means of the inductorium, without apparent result. Ether anesthesia was discontinued at 11: 30 a. m.

Stimulation (3: 40 p. m.).—The animal was able to walk one hour after the anesthesia had been discontinued and thereafter appeared to be in good condition except for slight weakness of the left front leg. Stimulation was carried out for ten seconds. With the beginning of stimulation there was a slow but powerful flexion of the neck in the midline. The pupils dilated, but no motions of the eyes were observed. With the cessation of stimulation, this flexion relaxed somewhat, but by no means completely. The animal appeared to be unconscious and made no move to alter the position.

Thirty-five seconds after the cessation of stimulation, without the tonic spasm of the neck having disappeared, there was gradual onset of rhythmic flexion and extension of the neck in the midline. In the ensuing four or five seconds, as the clonus increased in violence and somewhat in frequency, there was extension, successively, to the left foreleg, the left side of the trunk and the left hindleg. These clonic convulsive movements of the entire left side then continued apparently unchanged for one minute and thirty seconds. During this interval the contractions were found to have a frequency of 2.4 a second. After this phase of the clonic seizure had continued a minute and a half, there was extension to the right side of the body. No definite sequence or "march" could be made out on this side. Contractions appeared to begin, synchronous with those on the left, in the trunk and in both legs. These were of slight amplitude at the outset but attained full height during the time required for the first four or five contractions to take place. The generalized convulsion then lasted twenty seconds and wore off in a phase characterized by slowing of the clonus and diminution of the violence of the contractions. The animal breathed stertorously and lay apparently unconscious for perhaps one minute. During this interval there was evacuation of the bowels and bladder. Thereafter, the animal appeared to regain consciousness, raised its head and responded to the voice. Four minutes after the end of the convulsive

movements, the animal was able to stand. There was marked weakness of both left legs, which defeated the first attempts. This appeared to improve rapidly during the ensuing ten minutes.

The second and third periods of stimulation were carried out at intervals after recovery, with less complete seizures as a result.

EXPERIMENT 4.—An immature female mongrel of the collie type, weighing 7 Kg., was used.

Operation (9:45 a. m.).—The procedure was the same as in the last experiment, with implantation of the active electrode on the hindleg area of the motor cortex. In this case, as vessels were stimulated, a hand lens was used for observing them. No constriction or blanching was seen. Ether anesthesia was discontinued at 11 a. m.

Stimulation (3:45 p. m.).—The animal recovered from the anesthesia rapidly and, by the time of stimulation, walked actively about the room. There was no sign of weakness of the legs. Stimulation was produced for ten seconds. During the stimulation there was tonic contraction of the left hindleg and of the neck in the midline. These continued without the appearance of clonus, and without spread, for five seconds after the termination of stimulation. There followed, gradually, the appearance of rapid clonic movements (from 4 to 5 a second) in the left hindleg, which rapidly shifted to the left foreleg and the neck and thence to the right side of the body. The sequence took place so rapidly that "march," in the ordinary sense of the word, can scarcely be said to have been observed. After the spread to the right side of the body, however, the left leg showed much more violent contractions than the right, throughout the convulsion. The animal appeared to lose consciousness at the beginning of the convulsion. The pupils were widely dilated. Drooling and frothing occurred. Breathing was deep and spasmodic.

The convulsion lasted one minute and ten seconds. At the end of that time, the clonic movements had decreased in frequency from 4 or 5 to 2 or 3 a second. The attack wore off gradually, the violence of the contractions also declining as the seizure reached its termination. At the conclusion of the seizure the animal lay quietly, breathing deeply, and unconscious, for two and one-half minutes. During this period noxious stimuli evoked no response. Thereafter, the animal raised its head and took cognizance of its surroundings, as if awakening from sleep. It was coaxed to rise. It was able to sit up but not to stand four minutes after the termination of the seizure; it could stand seven minutes after the seizure and walk thirty seconds later. There was marked weakness of both left legs, chiefly of the foreleg, and the anmial swayed and fell to the left during the first minutes of walking.

The second and third stimulations, fifteen and twenty minutes, respectively, after the end of the convulsion, resulted only in "incomplete" attacks; clonus could be set up by stimulation of ten seconds but stopped almost immediately after cessation of the excitation.

Comment.—The value of the technic is that, considering the fact that there is no pain or apprehension on the part of the subject, one is able to observe the unanesthetized subject, hours or days after preparation, immediately before and after a seizure that is remarkably similar to that seen in epilepsy. There is a possibility that careful neurologic observation may, in repeated experiences with the same animal, give

clues to the identity of the "level" initiating an experimental epileptiform convulsion. In the limited experience of my colleagues and me the only observation bearing on this question is that in successive attempts to produce convulsions in animals, whether following the first by minutes or by days, we have never produced a seizure as complete as the first. This, together with the work of the Vogts,[26] who showed that electrical stimulation causes distinct degenerative changes in nerve cells, may favor the responsibility of subcortical levels.

It will be noted that, in addition to loss and regaining of consciousness and the appearance or increase of weakness on the side primarily affected, there are seen in these seizures several phenomena noted by many authors as accompanying the "complete seizure": "tonic"-"clonic" succession; restricted area of origin; dilatation of the pupils; drooling and frothing; stertorous breathing, and independence of the frequency of stimulation and the frequency of resulting contractions.

In view of recent work by the Gibbs, in which the brains of conscious cats were stimulated electrically, this last factor deserves further comment. Horsley and Schäfer showed that the seemingly tetanic contractions produced when the motor cortex was stimulated at a frequency, for instance, greater than 40 a second, were in reality contractions at a rate of approximately 10 a second. Increasing the frequency of stimulation had little effect on this secondary rate. When clonic contractions supervened, at a rate of, for instance, 3 or 4 a second, these in turn were formed by the summation of several contractions at the rate of about 10 a second. Gotch and Horsley, using a capillary electrometer, compared the electrical impulses traveling down the spinal cord of the cat and monkey during cortical stimulation with the frequency of the muscular clonus produced and found them the same. On account of these observations and the conclusions of François-Franck and Pitres, Bubnoff and Heidenhain and Horsley and Schäfer, who found it usually impossible to produce clonic convulsions by stimulation of subcortical levels, clonus has been considered a contribution of the motor cortex.

The Gibbs, using unipolar stimulation by means of an Adrian-Bronk needle, produced convulsions in cats with ease by stimulation of subcortical fiber tracts.[27] These were characterized, in part, by "a series of violent movements, continuing after stimulation, not purposeful in nature." Some criticism of their adaptation of the method may be made in that the outer surface of the hollow needle transmitting the active electrode was not coated with dielectric material. Depending on

26. Vogt, Cécile, and Vogt, O.: Erkrankungen der Grosshirnrinde, J. f. Psychol. u. Neurol. **28**:1, 1922.

27. Gibbs, Frederic A., and Gibbs, E. L.: The Convulsion Threshold of Various Parts of the Cat's Brain, Arch. Neurol. & Psychiat. **35**:109 (Jan.) 1936.

the depth of insertion, this surface may have stimulated to a greater or less degree, regardless of the fact that it was not connected directly with the source of current. However, if their use of the method proves to be beyond reproach, it may be necessary to reconsider a great deal of the work on epileptiform convulsions produced electrically.

SUMMARY

We have produced epileptiform convulsions in dogs by a method that allows observation of the complete attacks in unanesthetized, unrestrained subjects. These convulsions, which appear to approach those seen in clinical epilepsy more closely than experimental convulsions ordinarily produced by electrical stimulation, are described in detail.

CYSTIC TUMOR OF THE THIRD VENTRICLE CONTAINING COLLOID MATERIAL

HOWARD ZEITLIN, M.D.
AND
BEN W. LICHTENSTEIN, M.D.
CHICAGO

Of the different types of cystic tumor originating within the third ventricle (aside from cystic degeneration of a solid tumor and the epidermoid, the dermoid and the parasitic cyst), that containing colloid material arising from the most rostral end of the roof of the third ventricle is by far the most interesting and important. This cystic tumor, because of its distinct gross and microscopic appearance, has largely been referred to in the literature as "colloid cyst," and recently, because of the as yet uncertain origin and the nature of the content, it has been called "neuro-epithelial cyst" by Percival Bailey.

The frequent reports of cases of this cystic tumor in the recent literature are probably due to increasing knowledge of its clinical manifestations, to the almost pathognomonic significance of ventricular air studies (Dandy [1] and Davidoff and Dyke [2]) and to the successful surgical treatment (Dandy,[1] Davidoff and Dyke,[2] Stookey,[3] Masson,[4] Zimmerman and German [5] and Patterson and Leslie [6]).

We report the present two cases, first, because of the scarcity of complete clinicopathologic studies and, second, to prove that the structures observed within the cyst are identical with those present in the paraphysis of the human embryo and of lower vertebrates, thus substantiating the theory that this cyst is a derivative of the embryonic structures of the paraphysis.

From the Pathology Laboratories of the Cook County Hospital (Dr. R. H. Jaffé, Director) and the Division of Neuropathology (Dr. G. B. Hassin, Director), the University of Illinois College of Medicine.

1. Dandy, Walter E.: Benign Tumors in the Third Ventricle of the Brain: Diagnosis and Treatment, Springfield, Charles C. Thomas, Publisher, 1934.

2. Davidoff, L. M., and Dyke, C. M.: Congenital Tumors in the Rostral Portion of the Third Ventricle, Bull. Neurol. Inst. New York **4**:221, 1935.

3. Stookey, B.: Intermittent Obstruction of the Foramen of Monro by Neuro-epithelial Cysts of the Third Ventricle, Bull. Neurol. Inst. New York **3**:446, 1934.

4. Masson, C. B.: Complete Removal of Two Tumors of the Third Ventricle with Recovery, Arch. Surg. **28**:527 (March) 1934.

5. Zimmerman, H. M., and German, W. J.: Colloid Tumors of the Third Ventricle, Arch. Neurol. & Psychiat. **30**:309 (Aug.) 1933.

6. Patterson, J. E., and Leslie, M.: Colloid Cyst of Third Ventricle of the Brain: Report of a Case Operated on with Recovery, Brit. M. J. **1**:920, 1935.

REPORT OF CASES

CASE 1.—*Periodic attacks of headache for twelve years, associated with epileptiform seizures and hypersomnia. Large cystic tumor in the third ventricle containing colloid material. Microscopic diagnosis: paraphysial cyst.*

History.—L. J., a white woman aged 42, entered one of the medical services of the Cook County Hospital on Oct. 2, 1935, in a comatose condition. At that time no detailed history was obtained from her husband, who merely stated that she had had headaches for the past twelve years but that during the last year she had been troubled with "sleeping spells." On the day prior to entrance to the hospital she became more lethargic; she did not respond to questions and passed into coma.

Examination.—The patient was well developed; her face was flushed, and she was in deep coma. The temperature was 102 F., the pulse rate 112, the respiratory rate 24 and the blood pressure 160 systolic and 80 diastolic. The right pupil was slightly larger than the left; both reacted sluggishly to light. The lower extremities were held slightly rigid. Examination of the heart, lungs and abdominal organs revealed no abnormal changes.

The tendon reflexes were exaggerated throughout. Rossolimo and Chaddock signs were obtained bilaterally, but the Babinski sign was atypical. The patient responded slightly to deep pressure over the supra-orbital nerve. Examination of the fundi was not recorded.

Laboratory Data.—The spinal fluid was clear and under increased pressure; it contained 220 cells per cubic millimeter (polymorphonuclear cells and lymphocytes, in equal proportions). The Pandy reaction was strongly positive. The Wassermann reaction of both the blood and the spinal fluid was negative. The urine contained a trace of albumin.

Course.—The patient's condition remained poor. She did not respond to intravenous injections of dextrose and died on the day following entrance to the hospital.

Comment.—A tentative diagnosis of lethargic encephalitis was made, but a tumor of the brain was strongly considered. Only after necropsy had been performed were more complete data furnished by the patient's husband. He stated:

The patient had complained of headaches for the past twelve years, since the birth of her last child; these were later followed by sudden attacks of unconsciousness and periods of uncontrollable drowsiness. At the onset the headaches were more pronounced during the menstrual periods but were relieved by acetylsalicylic acid and recumbent posture. The attacks were not associated with nausea, vertigo or vomiting but grew steadily worse, and during the last year the pain had been constant. From 1925 to 1931 the patient was free from symptoms. Associated with the headaches were periods of sudden unconsciousness, with no premonitory symptoms. On one occasion, ten years before, while the patient was talking to a neighbor at the top of a staircase, she suddenly slid down the stairs. On another occasion she suddenly became unconscious and fell against a hot stove, burning her hand. She was known to have had a similar attack while in a grocery store. She fell asleep for short periods after these episodes and on awakening resumed her duties as usual, without realizing that anything had occurred. Years later the attacks of unconsciousness disappeared, except for momentary periods during which she was dazed, but did not fall, and her eyes "exhibited a peculiar, glassy stare." During the last five years she was troubled with attacks of uncontrollable drowsiness, which were so pronounced that she sometimes fell asleep in church or at the theater, or even while talking to friends. These periods became more

frequent until during the last two years she could hardly stay awake. During the periods of sleep she responded well and answered questions but went to sleep again in a short time. Her mental condition grew progressively worse during the last six months; she became absent minded; at times she was moody, and her memory became poor. She was slovenly in dress and personal habits. During the last few months she menstruated every two weeks and passed considerable clots of blood.

There were no signs of adiposity during the illness, nor were there any symptoms which suggested diabetes insipidus or diabetes mellitus.

Necropsy (Dr. R. H. Jaffé).—Gross Observations: The brain weighed 1,350 Gm. The convolutions were flattened, and the vessels at the base were thin walled. The meninges over the convexity were injected and in the region of the infundibulum were thickened and gray white. In the infundibular region the base of the brain was bulging, slightly compressing the hypophysial stalk.

On sectioning the brain, after fixation in a 10 per cent solution of formaldehyde U. S. P., the third and lateral ventricles were observed to be tremendously dilated. The third ventricle contained a well circumscribed, ovoid cystic tumor, measuring 5 by 4.5 by 3.5 cm. in its greatest diameters. The tumor was situated in the midline and was loosely attached to the roof of the third ventricle. The mass compressed both lateral ventricles, completely obliterated the septum pellucidum and occluded both intraventricular foramina of Monro. The cyst could be moved about easily and on its superior aspect was covered by the tela choroidea, which was composed of markedly dilated and thickened blood vessels. On its upper lateral aspects small portions of the choroid plexus were adherent to the wall.

The external surface of the cyst was smooth and was represented by a semitranslucent membrane, beneath which a dark mass shone through. The contents of the cyst consisted of a honey-like, homogeneous, deep brown material, of rubbery consistency. It separated easily from the wall, which was fairly thin throughout except for a circumscribed, light gray-brown nodule, which measured 5 by 2 mm. in diameter and was attached to the posterior aspect of the wall (fig. 1).

The corpus callosum and fornices were markedly compressed, as were also the optic thalami and the infundibular region. The latter area bulged in the direction of the hypophysial stalk. The brain tissue of the floor of the third ventricle and about its lower lateral aspects was softened. In some areas the softened brain tissue was loosely attached to the external surface of the cyst. Here and there small light purple-red, discolored areas were present in the regions of softening.

The pineal body and the pituitary gland were intact; no changes were seen in the sylvian aqueduct (fig. 1).

Microscopic Examination: The large cyst within the third ventricle was lined by a capsule of collagenous connective tissue, which varied in thickness and microscopic appearance. The capsule on its superior surface, which was attached to the tela choroidea, was markedly thickened; through its superior lateral surface it was attached to the choroid plexus (fig. 2). The inner aspect of the capsule was lined largely by a single layer of cuboidal cells, which in some areas revealed a basement membrane. For the most part the epithelial cells were flattened (fig. 3*A*), while in other areas they were several layers deep. The epithelial cells were characterized by large vesicular nuclei, in which were scattered for the most part fine, pale granules of chromatin. The nuclei were embedded in ample cytoplasm.

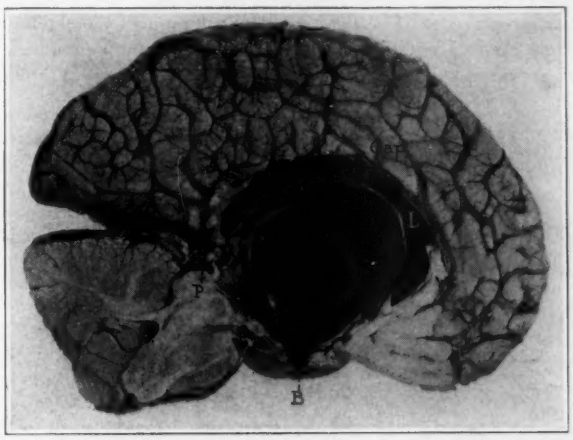


Fig. 1 (case 1).—Photograph showing a large cyst of the third ventricle containing colloid material and surrounded by a thin-walled capsule (*Cap*). The cyst protrudes into the anterior horn of the lateral ventricle (*L*). *P* indicates the pineal body, and *B*, the base of the third ventricle.

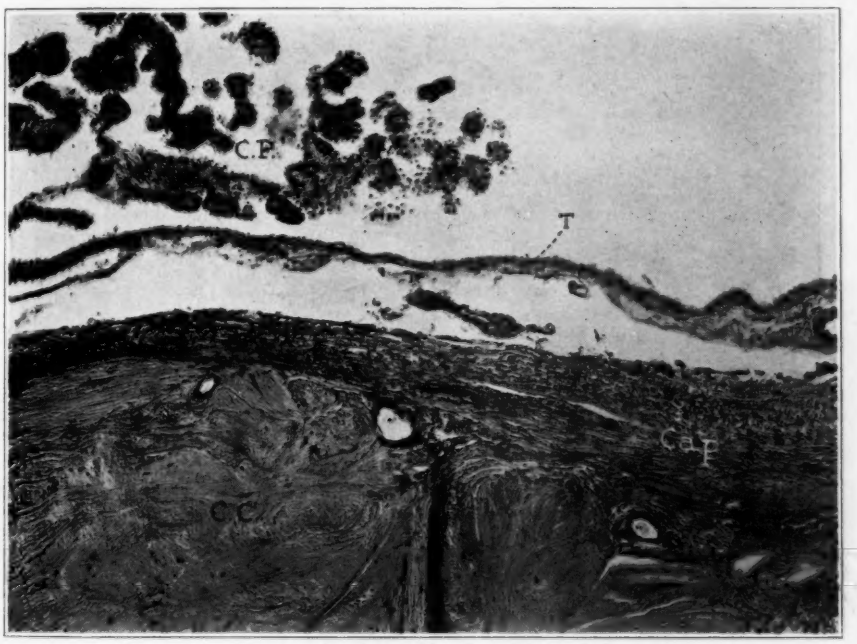


Fig. 2 (case 1).—Photomicrograph (Van Gieson stain; low power magnification) of a section showing the relation of the choroid plexus (*C. P.*) and the collagenous connective tissue capsule (*Cap*) to the outer wall of the cyst. *C. C.* indicates the colloid content of the cyst.

The boundaries of the cells, which resembled ependymal lining cells, were indistinct (fig. 3*B*). Blepharoplasts or cilia were not noted. Frequently the cells were swollen and contained no lipoid granules, but when stained with the method of Van Gieson, the cytoplasm appeared partially filled with light yellow-brown amorphous granules.

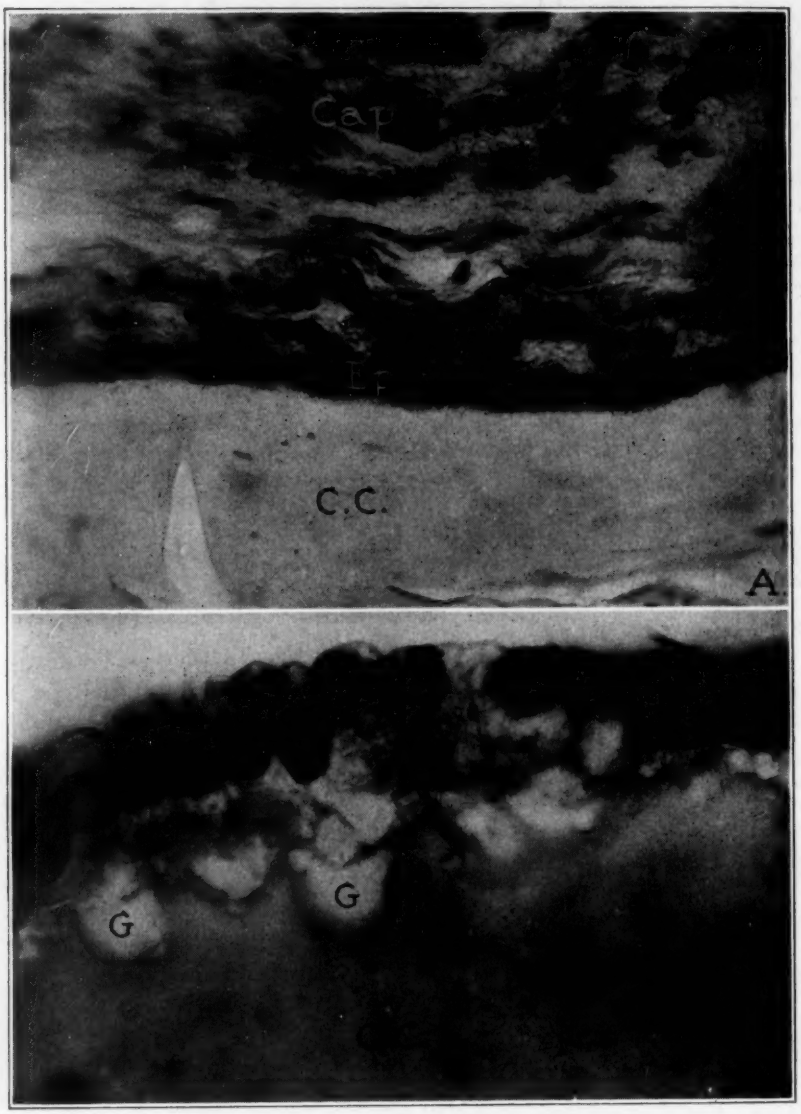


Fig. 3 (case 1).—Photomicrographs: *A* (high power magnification) shows (*Ep*) the innermost layer of flattened epithelial lining cells; *Cap*, the connective tissue capsule, and *C. C.*, the colloid content of the cyst. *B* (oil immersion magnification; Van Gieson stain) shows the vacuolated appearance of the layer of epithelial lining cells separated from its connective tissue wall; *C. C.*, the colloid contents, and *G*, the small, sprouting globules.

On the inner surface of the swollen epithelial cells bordering the cystic contents were observed small sprouting spherical globules (fig. 3*G*), which gave them frequently the appearance of active secreting cells.

The contents of the cyst consisted of a structureless, homogeneous colloid substance, which stained light pink with hematoxylin and eosin and orange yellow with the method of Van Gieson (fig. 3, *C. C.*).

In various areas of the capsule, especially in the region of its thickened superior upper portion, there were groups of small and large tubules. The lumens of the larger tubules were filled with colloid material, resembling secondary cyst formations, and were lined by a single layer of cuboidal cells. Their cell boundaries were indistinct, and in general the cells had the features that have already been described (figs. 4 and 5). In structure these groups of small tubules resembled slightly glandular formation.

Secondary Changes: These consisted of marked chronic inflammatory infiltrations and degenerative processes. In some areas numerous capillary blood vessels extended for a short distance from the wall of the cyst into the colloid contents. About these vessels there were large, old and recent hemorrhages. There were also dense perivascular accumulations of plasma cells, fibroblasts and histiocytes filled with yellow-brown pigment. These cells extended irregularly beyond the walls of the vessels. At the periphery of the latter areas were observed masses of fibrin, necrotic cellular débris and large vacuolated cells filled with sudanophilic material. These changes were also present in the capsule of the cyst, particularly within its thickened upper portion. Frequently the histiocytes filled with lipoid material were seen among the epithelial lining cells, often displacing them and appearing as a single layer of large goblet cells.

Polariscopic examination revealed double refractile bodies, in the nature of fatty acid crystals and cholesterol esters. Numerous clefts were filled with long, rhombic crystals of the foreign body type, to which were attached giant cells. In one area calcification and bone formation were noted.

Sections taken from the various parts of the brain and stained with toluidine blue revealed marked changes in the parenchyma of the brain surrounding the third ventricle. Particularly striking were the changes in the ganglion and the glia cells in the regions adjacent to the wall of the cyst. In the region of the hypothalamus the large ganglion cells exhibited extensive regressive changes in the nature of severe ischemic cell changes. The surrounding interstitial cells were increased in number and were mainly microglia cells and cytoplasmic astrocytes. In focal areas beneath the ependyma and in the region of the substantia nigra, there were small areas of recent extravasations of blood. The capillaries in these areas showed swollen adventitial cells and occasionally were surrounded by histiocytes filled with greenish-brown pigment granules. The meninges over the cerebral hemispheres and at the base were thickened and fibrosed and were loosely infiltrated with large mononuclear cells filled with greenish pigment granules. The architecture of the cerebral cortex was not affected.

The choroid plexus and the pineal body revealed no particular histologic changes. The tuft cells of the plexus adjacent to the outer surface of the capsule consisted of a single layer of cells with distinct cell boundaries, containing small, round nuclei with coarse, deeply staining chromatin granules. The tuft cells differed distinctly from the epithelial cells that lined the cystic tumor.

CASE 2.—*Headaches for five years; sudden onset of severe headaches associated with vomiting, followed by complete recovery. Similar attack five weeks later, associated with hypersomnia. Large cystic tumor in the third ventricle containing colloid material. Microscopic diagnosis: paraphysial cyst.*

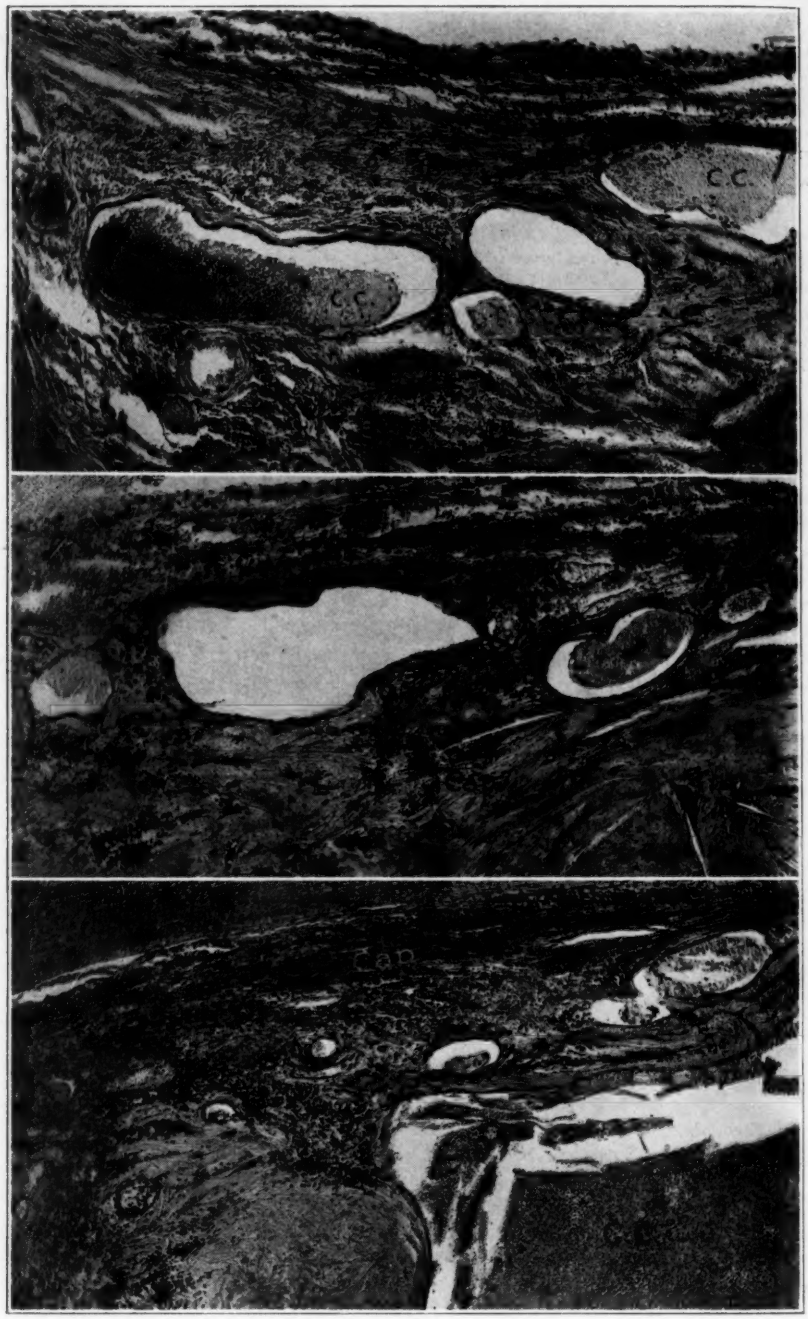


Fig. 4 (case 1).—Photomicrographs (Van Gieson stain; low power magnification) showing numerous tubules and small secondary cyst formations lined by flattened epithelial cells. The thickened capsule wall (*Cap*) is markedly infiltrated with chronic inflammatory cells; *C. C.* signifies the colloid content within the small and large cysts.

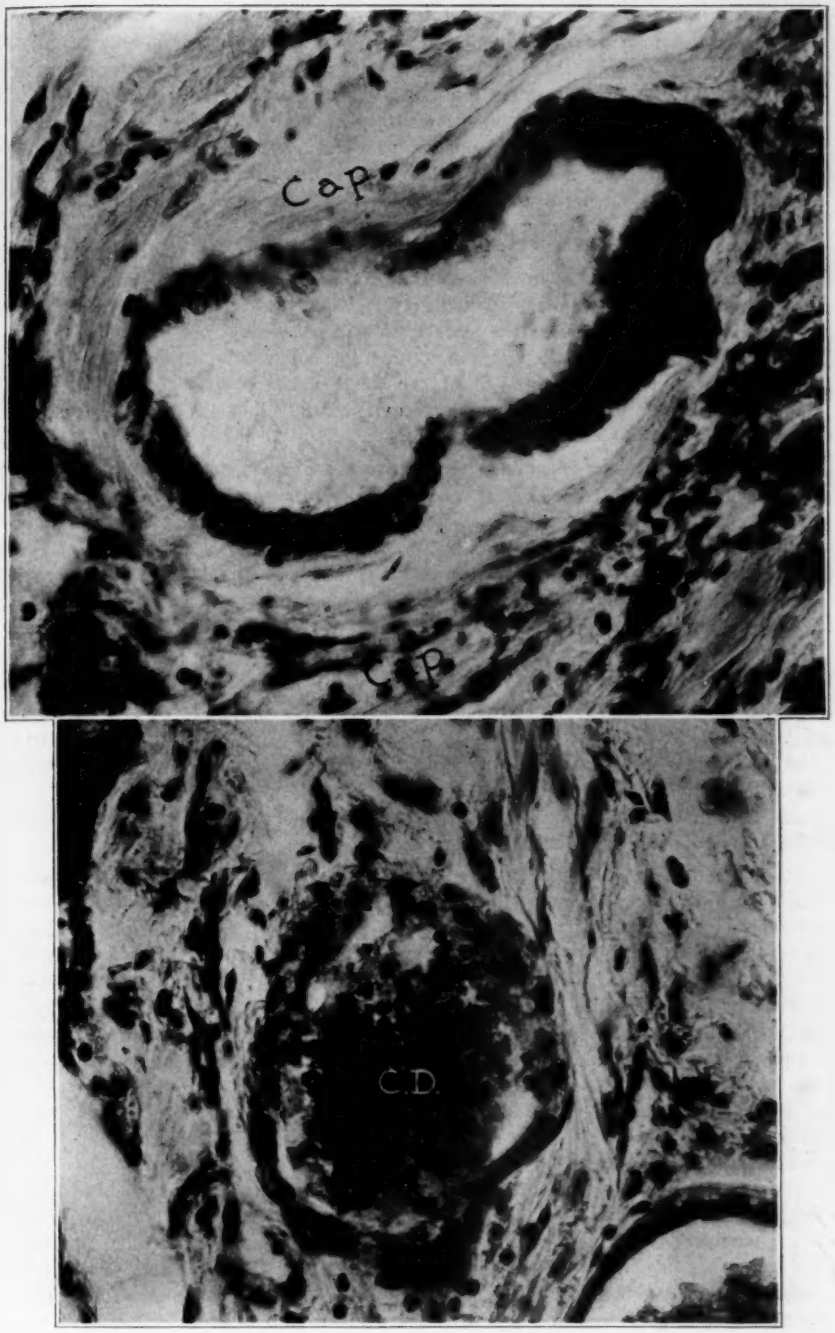


Fig. 5 (case 1).—Tubules lined by epithelial cells within the thickened capsule wall of the cyst (Van Gieson stain; high power magnification). *C. D.* indicates the lumen filled with cellular débris.

History.—A man was brought in a semiconscious state to the Woodlawn Hospital, under the care of Dr. Clinton A. Elliott, who gave us the opportunity to study this case. A brother stated that for the last five years the patient had been troubled with headaches, which were frequently associated with vomiting. He was described as having a "shut-in personality"; he had never troubled his family with his complaints until six weeks before his admission, when he was awakened from sleep by a severe, splitting headache, which continued for several hours. After this incident he felt weak and often staggered when he walked. However, he was able to resume his clerical work for the next five weeks. On the day of admission to the hospital he was again awakened by a violent headache, accompanied by nausea and projectile vomiting, which recurred on the attempt to swallow anything. He lapsed into a comatose state from which he could not be aroused until several hours later, when he passed a considerable amount of urine.

The patient had always been stout; he weighed 243 pounds (110.2 Kg.). In the past year he had dieted strenuously and faithfully, but his weight remained the same.

Examination.—The patient was semiconscious; his temperature and the pulse and respiratory rates were normal, and the blood pressure was 128 systolic and 88 diastolic. Examination of the chest and abdominal viscera revealed nothing abnormal.

The pupils were equal and reacted to light and in accommodation. All tendon reflexes were hyperactive. The abdominal reflexes were not elicited; Babinski reflexes were obtained bilaterally. The fundi of the eyes on the first day of observation were essentially normal; on the following day there was blurring of the disk margins, and on the fourth day the disks revealed bilateral papilledema.

Laboratory Data.—The spinal fluid was clear and under a pressure of 450 mm. of water; the reaction to the test for globulin was negative. The Wassermann reaction of both the blood and the spinal fluid was negative. The blood count, as well as the blood chemistry, was within normal limits.

A roentgenogram of the skull revealed no definite pathologic changes. The sella turcica appeared normal.

Course.—During the patient's stay in the hospital he exhibited an uncontrollable desire to sleep, which lasted through the day and night. The periods of sleep were peculiar, in that he could often be aroused easily and readily answered questions directed to him. At other times he could not be aroused. He ate fairly well but frequently vomited a short time after eating. On several occasions he was incontinent and voided large quantities of urine; frequently, however, he had to be catheterized. Ventriculography was considered, but the patient lapsed into deep coma on the eighth day; the pupils failed to react to light; the knee jerks could not be elicited; the neck became rigid, and respiration of the Cheyne-Stokes type developed. The patient died nine days after entrance to the hospital, and eight weeks after the onset of marked symptoms. A diagnosis of tumor of the brain (cerebellar or intraventricular) was made.

After necropsy, the following history was obtained: In addition to headaches, the patient always seemed tired and exhausted and perspired freely. It was noted that particularly after eating a heavy meal he became drowsy and went immediately to bed, only to awaken in the morning feeling "groggy" and tired. The patient's mother, whom he had visited on Sundays for the past year, stated that he spent the greater part of that day sleeping.

A friend related an incident to the family that had occurred about nine months before. While he was walking with the patient along the railway tracks, the patient,

for no apparent reason, suddenly collapsed and fell to the ground. When assisted to his feet, he stated that he felt as though he had fallen into a hole.

Necropsy (Dr. J. Kirshbaum).—Gross Observations: The essential pathologic changes were observed in the brain, which weighed 1,300 Gm. The convolutions were flattened; the floor of the third ventricle was markedly thinned and bulging, compressing the region of the tuber cinereum. Coronal sections of the brain revealed a large cystic tumor, measuring 30 by 25 by 25 mm., occupying the third ventricle, which was markedly dilated as were also the lateral ventricles (fig. 6). The tumor was attached to the rostral portion of the roof of the third ventricle and to the fornices (fig. 7*F*). It completely occluded the intraventricular foramina of Monro, and the septum pellucidum was almost obliterated. The tumor formed a niche in the rostral portion of the floor of the third ventricle, which there appeared semitransparent. The corpus callosum above the cyst was markedly thinned, and the thalami were likewise compressed. The sylvian aqueduct and the fourth ventricle were not dilated. The choroid plexus was attached to the superior

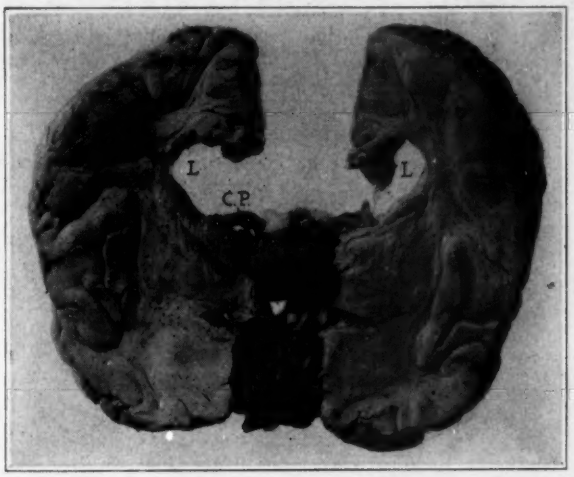


Fig. 6 (case 2).—Photograph of a cystic tumor attached to the rostral portion of the roof of the third ventricle and to the fornices, at *F*, and occupying the dilated third ventricle. *C. P.* shows the choroid plexus attached to the superior lateral wall of the cyst, and *L*, the dilated lateral ventricle; the walls of the thalamus are compressed.

lateral surface of both sides of the cyst and extended into the lateral ventricles (fig. 6, *C. P.*). The capsule of the cyst was smooth, light yellow-gray and translucent. When the cyst was sectioned after fixation, the contents were observed to be gelatinous and of a soft, rubbery consistency; they could easily be separated from the capsule (fig. 7, *C. C.*). There was a light gray node, measuring 4 by 4 mm., which extended from the lateral inner surface of the capsule into the contents of the cyst.

Microscopic Examination: The wall of the cystic tumor was represented by vascular connective tissue that was lined on its inner surface by a layer of cuboidal or columnar cells. Frequently the inner layer was from two to three cells deep, but for the most part it consisted of a single layer of epithelial cells with indistinct cell boundaries (fig. 9*B*); the cytoplasm of these epithelial cells often appeared vacuolated; their nuclei were round or oval and contained loosely scattered, fine

chromatin granules, resembling those of ependymal cells. The superior surface of the capsule of the cyst blended with the tela choroidea, which separated the parenchyma of the brain from the inner epithelial lining cells. The tela choroidea completely enveloped the cyst, forming the outer, connective tissue, layer of the capsule. The choroid plexus was attached to both the superior and the lateral aspect of the wall of the cyst (fig. 7, *C. P.*).

In one area the epithelial cells were markedly proliferated and formed a solid layer of cells. The cell boundaries were indistinct and extended for a short distance into the contents of the cyst. In this area, as well as in other parts of the capsule,

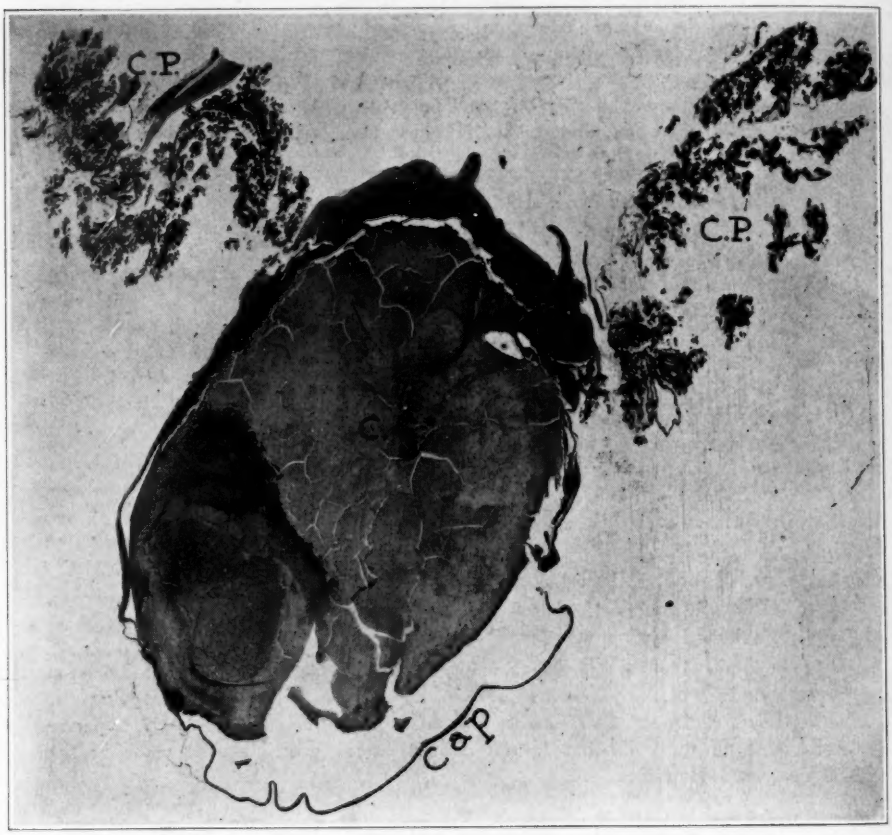


Fig. 7 (case 2).—Photomicrograph (Van Gieson stain; low magnification) showing an encapsulated cyst attached to the fornix (*F*). *C. P.* indicates the choroid plexus attached to the superior portion of the outer wall; *C. C.*, the colloid content of the cyst, and *Cap*, the capsule.

distinct tubules were observed. The tubules were lined by a single layer of cuboidal or columnar cells similar to those that lined the large main cyst (figs. 8 and 9*A*); occasionally their lumens contained desquamated cellular material. Blepharoplasts and cilia were not observed. When studied in longitudinal sections the tubules resembled renal tubules (fig. 8*C*). The contents of the cyst resembled colloid and stained homogeneously light pink with hematoxylin and eosin and light yellow brown with the method of Van Gieson.

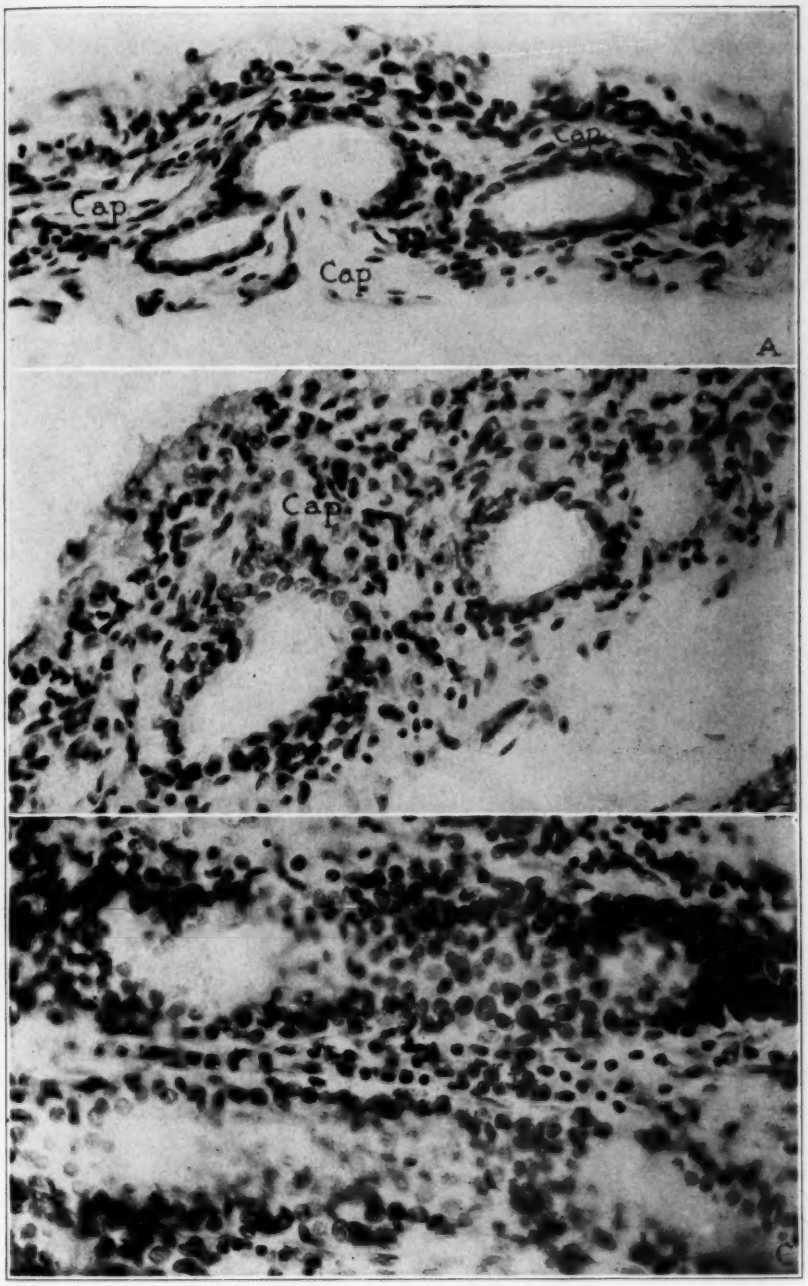


Fig. 8 (case 2).—*A* and *B* show small tubules lined by a single layer of columnar epithelial cells, and *C* shows tubules cut tangentially, resembling formations of renal tubules (hemalum stain; high power magnification). *In* indicates inflammatory cells, and *Cap*, the capsule.

The small node which extended from the capsule into the contents of the cyst consisted of a mass of desquamated cells, devoid of cytoplasm, but the nuclei were distinct and appeared homogeneous.

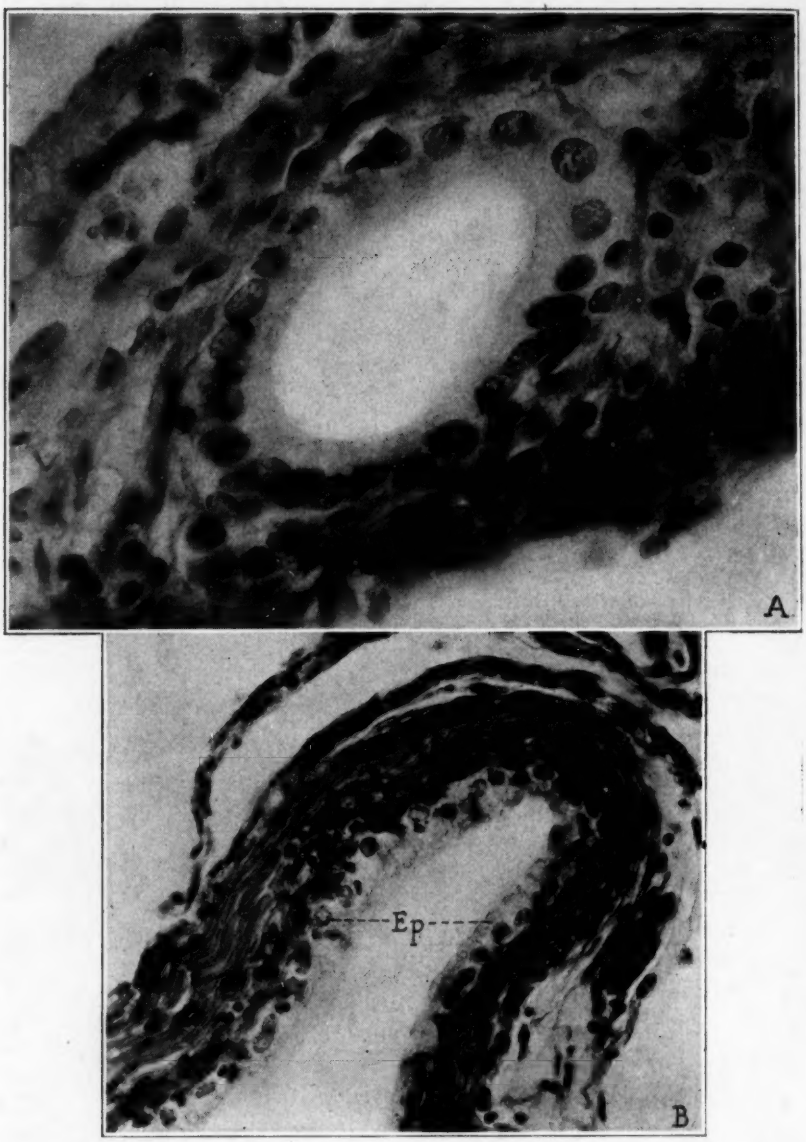


Fig. 9 (case 2).—Photomicrographs: *A* (oil immersion shows formation of tubules, and *B* (high power magnification; Van Gieson stain) the capsule wall separated from the contents of the cyst and lined by a single layer of columnar cells (*Ep*). The cell boundaries are indistinct.

Secondary changes in the cyst were in the nature of an acute inflammatory cellular reaction. Numerous polymorphonuclear cells, histiocytes and lymphocytes invaded the capsule and the contents of the cyst, often obscuring the lining epithelial cells. Sections stained with sudan III failed to disclose any lipoid substance within the cystoplasm of the epithelial cells, but lipoid was frequently observed in the histiocytes among the epithelial elements.

Sections taken from various parts of the brain revealed the most marked changes in the structures surrounding the third ventricle. In the fornices, which were adherent to the superior aspect of the cyst, there were marked perivascular accumulations of small lymphocytes. The adventitial cells about the smaller blood vessels were much swollen. Many of the glia cells were transformed into cytoplasmic glia cells. The ganglion cells in the hypothalamic nuclei and in the basal ganglia revealed severe ischemic changes. Just beneath the ependymal cells lining the third ventricle there were accumulations of moderately large, round, homogeneous, light blue bodies (*Abbau* products). The meninges over the cerebral hemisphere were thickened and fibrosed; at the base of the brain, especially in the infundibular region, they were loosely infiltrated with lymphocytes.

COMMENT

Depending on the size and location, a cystic tumor of the third ventricle may cause no symptoms. This is the case when the cyst is small and freely suspended from the roof of the third ventricle. When symptoms are present, they may be fairly characteristic. As the cyst gradually increases in size, it causes partial or complete occlusion of the foramina of Monro, which in turn interferes with the passage of cerebrospinal fluid and, by compressing the veins of Galen at their origin, with the venous return from the choroid plexus of the lateral and third ventricles. Other associated symptoms are due to pressure on the adjacent hypothalamic nuclei and tracts.

Frequently, when the cyst is not firmly attached to the roof of the third ventricle and is freely movable, it may cause a ball and valve action by repeated temporary occlusions of the foramina and thus may lead to intermittent or paroxysmal symptoms. Likewise, symptoms may be produced by posture and tilting of the head, as was noted in the cases reported by Weisenburg [7] and Fulton and Bailey.[8] On the other hand, the cyst may suddenly become impacted into the foramina of Monro and lead to sudden death (Drennan [9] and Rinder and Cannon [10]). In the absence of permanent occlusion, the gradually increasing, incomplete internal hydrocephalus, together with the growing volume of the

7. Weisenburg, T. H.: Tumors of the Third Ventricle with the Establishment of a Symptom-Complex, Brain **33**:236, 1910.

8. Fulton, J. F., and Bailey, P.: Tumors in the Region of the Third Ventricle: Their Diagnosis and Relation to Pathological Sleep, J. Nerv. & Ment. Dis. **69**:1, 1929.

9. Drennan, A. M.: Impacted Cyst in Third Ventricle of the Brain: Report of Two Cases, Brit. M. J. **2**:47 (July 13) 1929.

10. Rinder, C. O., and Cannon, P. R.: Impaction of a Neuroepithelial Cyst in the Third Ventricle of the Brain, Arch. Neurol. & Psychiat. **30**:880 (Oct.) 1933.

cyst, causes obliteration of the septum pellucidum and of the intraventricular foramina. When the cyst becomes so large that it encroaches on the so-called sleep-regulating center in the floor of the third ventricle (Sahlgren [11]) or "the substantia reticularis on either side of the foramen of Monro" (Laruelle [12]), additional characteristic symptoms become manifest, in the nature of hypersomnia.

The intermittency of symptoms, extending over twelve years in case 1, and the sudden, severe onset of symptoms followed by remissions, in case 2, correspond with the anatomic considerations mentioned. Of particular interest are the periods of sudden onset of unconsciousness, or what has been referred to as epileptiform seizures by Högner [13] and Hassin and Anderson.[14] Likewise, the periods of hypersomnia uncontrollable desire to sleep, which are due to pressure of the cyst on the hypothalamic nuclei and the floor of the third ventricle and which were pronounced features in both our cases, are of practical clinical importance. Guillain, Bertrand and Périsson [15] reported a similar case in which hypersomnia, hyperthermia and polyuria were present during the attacks. The hypersomnia associated with cysts of the third ventricle has been considered analogous to physiologic sleep by Fulton and Bailey [8] and differs from the somnolence and stupor that develop in the course of intracranial pressure. In both our cases the patients could easily be aroused and occasionally responded to questions but went to sleep again in a short time.

Although from the clinical point of view an antemortem diagnosis is difficult to make, the proper morbid condition may be suggested by the recurrence of certain symptoms, such as a tendency to intermittent attacks, sudden onset of violent headaches associated with vomiting lasting several hours and recurring after a period of relative freedom from symptoms, relief from symptoms by change of posture, epileptiform seizures, hypersomnia, paresthesias and visual disturbances. The aforementioned symptoms and signs may lead to early recognition of the cyst and thus, undoubtedly, contribute to its successful surgical treatment, especially since it is possible to identify the cyst by means of ventriculography.

---

11. Sahlgren, Ernst: Experimentelle Untersuchungen über den Angriffspunkt des Luminals im Gehirn bei Kaninchen, Acta psychiat. et neurol. **9**:129, 1934.

12. Laruelle, L.: The Vegetative Centers of the Median Diencephalon, Rev. neurol. **1**:809, 1934; abstr., Arch. Neurol. & Psychiat. **35**:191 (Jan.) 1936.

13. Högner, P.: Die klinischen Erscheinungen bei Erkrankungen des dritten Gehirnventrikels und seiner Wandungen, Deutsche Ztschr. f. Nervenh. **97**:238, 1927.

14. Hassin, George B., and Anderson, J. B.: Cystic Tumor of the Third Ventricle, U. S. Vet. Bur. M. Bull. **6**:56, 1930.

15. Guillain, G.; Bertrand, I., and Périsson, J.: Etude anatomo-clinique d'une tumeur du troisième ventricule, Rev. neurol. **41**:467, 1925.

Pathologic Considerations.—Early reviews of the subject of tumor of the third ventricle by Weisenburg,[7] Högner [13] and Fulton and Bailey [8] dealt largely with the symptomatology and the attempt to establish a symptom complex. More recent literature has emphasized particularly the pneumo-encephalographic findings and the surgical management of the true intraventricular cystic tumor arising from the rostral portion of the roof of the third ventricle. Little has been written about the origin of this cyst and its pathologic features.

In the approximately fifty cases of so-called colloid cyst which have been reported, the origin has been variously traced to the choroid plexus, to the fetal ependyma and, as first suggested by Sjövall,[16] to the paraphysis.

The close attachment of the "colloid cyst" to the choroid plexus can perhaps best be explained by considering the origin of the choroid plexus. In the embryo, the choroid plexus arises from the paraphysial arch, which gives rise to the plexus of the lateral ventricles, and from the postvelar arch, which gives rise to the plexus of the third ventricle. In other words, the choroid plexus arises from the anterior and the posterior end of the velum transversum. The paraphysis takes origin immediately in front of the velum transversum, so that the rudimentary paraphysis is surrounded by the choroid plexus. The absence of similar cysts containing colloid material in the lateral and fourth ventricles of the brain would speak against the possible derivation of this cyst from the choroid plexus. In cases of true cyst arising from the choroid plexus observed in the autopsy material of the Cook County Hospital and the Research and Educational Hospital of the University of Illinois fairly characteristic gross and microscopic features were exhibited. The cyst has a transparent wall and is filled with clear, watery fluid. It contains a weblike network of delicate connective tissue strands, and about the wall calcareous bodies are observed. Such a cyst of the choroid plexus resembles neither grossly nor microscopically the colloid cyst of the third ventricle. Likewise, the cystic dilatation of the cavum septi pellucidi and that of the cavum Vergae recently described by Dandy [17] and Van Wagenen and Aird [18] are not to be confused with the cyst containing colloid material.

---

16. Sjövall, E.: Ueber eine Ependymcyste embryonalen Charakters (Paraphyse?) im dritten Hirnventrikel mit tödlichem Ausgang, Beitr. z. path. Anat. u. z. allg. Path. **47**:248, 1910.

17. Dandy, W. E.: Congenital Cerebral Cysts of the Cavum Septi Pellucidi (Fifth Ventricle) and Cavum Vergae (Sixth Ventricle): Diagnosis and Treatment, Arch. Neurol. & Psychiat. **25**:44 (Jan.) 1931.

18. Van Wagenen, W. P., and Aird, R. B.: Dilatations of the Cavity of the Septum Pellucidum and Cavum Vergae: Report of Cases, Am. J. Cancer **20**:539, 1934.

Frequently this cystic tumor is freely movable, except for the attachment to the choroid plexus, in the rostral portion of the roof of the third ventricle. In other cases it may be anchored, as in case 2, in which the cyst was firmly attached to the tela choroidea and, in turn, to the fornices of the brain (fig. 7 *F*).

Other investigators have identified blepharoplasts and ciliated epithelium in the epithelial lining cells of this cystic tumor and have shown their similarity to fetal ependymal cells. The observation of cilia by Sjövall,[16] Stookey,[3] Byrom and Russell [19] and other authors has not been held as conclusive evidence that the cyst is of ependymal origin, for in the embryo the cells covering the choroid plexus also possess cilia.

Sjövall,[16] because of the anatomic position of the cyst in his case and the character of the epithelial lining cells, first suggested the possibility, with a question, that this colloid cyst may arise from the paraphysis. The paraphysis was first described by Selenka [20] in lower vertebrates as an embryonic structure arising from the rostralmost portion of the roof of the third ventricle. From studies of the origin and development of the paraphysis in lower vertebrates, Warren,[21] Minot,[22] Dendy,[23] Eycleshymer and Davis,[24] Osborn [25] and Herrick [26] have concluded that the paraphysis is a structure common to all vertebrates, either in the adult or in the embryo. The paraphysis ascends steadily in its development from the cyclostomes, reaches its height in the urodeles and descends through the reptiles and birds to mammals. It develops from the telencephalon immediately cephalad to the velum transversum as a small diverticulum, from which a number of tubules are given off, which vary in size and shape and become eventually a complicated gland, with anastomosing tubules. The lining of these tubules consists of a single layer of short columnar cells, with indistinct cell boundaries. The spaces between the tubules are occupied by blood vessels, forming a sinusoidal circulation (fig. 10, *T*).

19. Byrom, F. B., and Russell, D. S.: Ependymal Cyst of the Third Ventricle, Lancet **2**:278 (Aug. 6) 1932.

20. Selenka, E.: Das Stirnorgan des Wirbelthiere, Biol. Centralbl. **10**:323, 1891.

21. Warren, John: The Development of the Paraphysis and the Pineal Region in Necturus Maculatus, Am. J. Anat. **5**:1, 1906.

22. Minot, C. S.: On the Morphology of the Pineal Region Based upon Its Development in Acanthias, Am. J. Anat. **1**:81, 1901-1902.

23. Dendy, A.: On the Development of the Parietal Eye and Adjacent Organs in Sphenodon (Hatteria), Quart. J. Micr. Sc. **42**:111 (Feb.) 1899.

24. Eycleshymer, A. C., and Davis, B. M.: The Early Development of the Paraphysis and Epiphysis in Amia, J. Comp. Neurol. **7**:45, 1897.

25. Osborn, H. F.: Contribution to the Internal Structure of the Amphibian Brain, J. Morphol. **2**:51, 1888.

26. Herrick, C. L.: Topography and Histology of the Brain of Certain Reptiles, J. Comp. Neurol. **1**:37, 1891; **3**:77, 1893.

Dexter,[27] in his work on development of the paraphysis in the fowl, described a formation of venules lined internally by a layer of cells. A cavity was filled with coagulum, and frequently spherical bodies were noted adjacent to the inner cell layer.

Francotte [28] in 1894 definitely identified the paraphysis in a human embryo of 12 weeks. The paraphysis appeared as an irregular tube and was situated deeply in the primitive cerebral falx in the median plane, in front of the lamina terminalis. The irregular tube was lined by a layer of cells of the original neural tube. Francotte stated that topographically it possessed all the characteristics observed in the paraphysis of the animal series. Bailey,[29] on the other hand, in a 19 mm. human embryo identified the paraphysial arch immediately in front of the

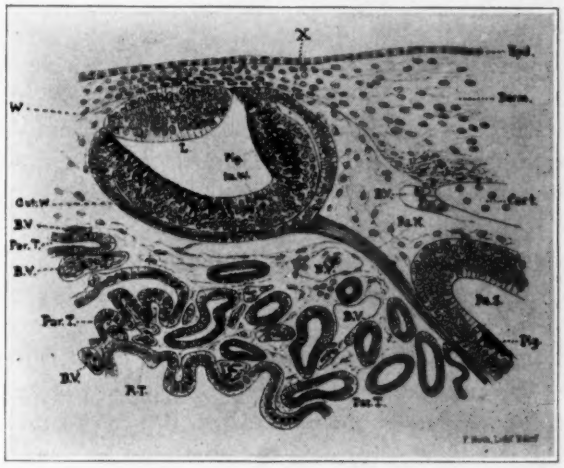


Fig. 10 (case 2).—Drawing (from Dendy [28]) of the paraphysial gland in Sphenodon, composed of numerous small and large tubule formations (*Par. T.*). *B. V.* indicates blood vessels. This picture should be compared with figure 8.

velum transversum but did not note any indication of the development of a glandular structure.

The microscopic structure of the tubules in the wall of the cyst in our cases is identical with that of the tubules of the paraphysis described in the lower vertebrates and in the human embryo. These tubules were

27. Dexter, F.: The Development of the Paraphysis in the Common Fowl, Am. J. Anat. **2**:13, 1902-1903.

28. Francotte, P.: Note sur l'oeil pariétal de l'épiphysis, la paraphysis et les plexus choroïdes du troisième ventricule, Bull. Acad. roy. d. sc. de Belgique **27**:84, 1894.

29. Bailey, Percival: Morphology of the Roof Plate of the Fore Brain and the Lateral Choroid Plexuses in the Human Embryo, J. Comp. Neurol. **26**:79, 1916.

particularly striking in the thickened superior surface of the capsule in case 1, in which the larger tubules contained colloid material similar to that in the main cyst. The larger tubules formed distinct, small secondary cysts. The presence of tubules in other areas about the wall of the cyst can probably be explained by the development of a single large cyst surrounded at the periphery by numerous tubules. As the cyst enlarges it carries along the small tubules in its vicinity.

In the past the origin from the paraphysis of this cyst of the third ventricle was suggested because of the precise anatomic position and the distinct biologic character of the contents—the colloid substance which has not yet been observed in cysts located elsewhere in the brain. The additional morphologic characteristics described in this paper definitely establish, in our opinion, the origin of this cyst from embryonic rests of the paraphysis.

With respect to the failure to demonstrate blepharoplasts and cilia in our cases, we believe that these structures were present during the earlier stages of cyst formation but later probably were destroyed by the severe inflammatory process (chronic in case 1 and acute in case 2) and the pressure produced by the contents of the cyst, as evidenced by the flatness of the epithelial cells.

The tubular formations and the morphologic features of the epithelial cells suggest the probability of the glandular character of these cysts and the secretory nature of their epithelial lining. Sjövall [16] first attempted to base the secretory nature of these epithelial cells on the presence in their cytoplasm of lipochrome granules, which stained with scarlet red. He expressed the belief that these lipochrome granules were definitely secretory. In our cases we failed to demonstrate lipochrome granules within the cytoplasm of the epithelial lining cells, but we frequently observed them within histiocytes which were present between the epithelial cells, often displacing them and occasionally forming a single layer between the connective tissue capsule and the contents of the cyst. These histiocytes were frequently ballooned, forming goblet-like cells and thus resembling secretory cells. However, the real secretory character of the epithelial cells in our cases was evidenced by the swollen cells, which often appeared vacuolated, with spherical globules adjacent to the inner surface of the epithelial cells and sprouting into the contents of the cyst (fig. 3 *B*).

Being a derivative of embryonic structures of the paraphysis, the so-called cyst of the third ventricle should be designated as a paraphysial cyst. It is interesting to note that Minot,[22] who investigated the paraphysis in lower vertebrates, predicted in 1901 that pathologic studies would enable one to demonstrate the presence of this organ in man.

The anatomic continuity of this cyst with the tela choroidea suggests that the connective tissue fibers in the wall are derived from the tela. The unusual large size of the cyst in case 1 was probably due partly to the repeated hemorrhages into the cyst.

The biologic character and physiochemical properties of the colloid substance within the cyst have not yet been studied. It would be of interest to analyze the contents at the time of operation, prior to fixation in formaldehyde, for possible hormonal substances and the like.

SUMMARY

1. Clinical and pathologic observations are reported in two cases of cystic tumor of the third ventricle of the brain containing colloid material.

2. Characteristic structures in the form of small tubules were observed in the walls of these cysts which are similar to the tubules described in the paraphysial gland of the human embryo and of lower vertebrates.

3. It is suggested that this cyst, which has been described as colloid cyst and as neuro-epithelial cyst of the third ventricle, be named paraphysial cyst.

EXPERIMENTAL STUDIES OF SERUM LIPASE IN MULTIPLE SCLEROSIS

KENNETH C. SWAN, M.D.
AND
HAROLD B. MYERS, M.D.†
PORTLAND, ORE.

In 1909 Marburg [1] suggested the possibility of an abnormal lipolytic ferment in the blood acting destructively on the myelin sheaths in multiple sclerosis. This possibility received added weight when Brickner [2] reported that the plasma of patients with multiple sclerosis produces a greater degree of myelolysis of the spinal cords of rats in vitro than does normal plasma. Weil and Cleveland [3] expressed the belief that the reaction is not sufficiently marked to be of etiologic significance. Crandall and Cherry [4] found that 78 per cent of patients with multiple sclerosis had in their serums an abnormal lipase which would split olive oil. The serums of an equally high percentage of patients with hepatic or pancreatic disease split olive oil, with even greater facility. This abnormal lipolytic activity could be produced experimentally in dogs by damage to the liver or pancreas. Brickner [5] reported that the values for serum esterase were normal only during clinical activity of the disease and that patients with clinically inactive disease had values higher than normal. Weil and Luhan [6] reported finding a myelolytic substance in the urine of a large number of patients with multiple sclero-

† Dr. Myers died on March 16, 1937.

From the Department of Pharmacology, University of Oregon Medical School.

1. Marburg, O.: New Contributions to the Problem of Multiple Sclerosis with Investigations on the Abdominal Reflexes, Wien. med. Wchnschr. **59**:2147, 1909.

2. Brickner, R.: Studies on the Pathogenesis of Multiple Sclerosis, Arch. Neurol. & Psychiat. **23**:715 (April) 1930.

3. Weil, A., and Cleveland, D.: A Serologic Study of Multiple Sclerosis, Arch. Neurol. & Psychiat. **27**:375 (Feb.) 1932.

4. Crandall, L., and Cherry, I.: Blood Lipase, Diastase, and Esterase in Multiple Sclerosis: Possible Index of Liver Dysfunction, Arch. Neurol. & Psychiat. **27**:367 (Feb.) 1932.

5. Brickner, R.: Esterasic Properties of the Blood in Cases of Multiple Sclerosis, Arch. Neurol. & Psychiat. **34**:466 (Aug.) 1935.

6. Weil, A., and Luhan, J.: Demonstration of Myelolytic Substances in the Urine of Patients with Multiple Sclerosis, Arch. Neurol. & Psychiat. **34**:458 (July) 1935.

sis. Recently Greco [7] has been unable to confirm the finding of an abnormal lipolytic activity of either the serum or the spinal fluid of patients with multiple sclerosis.

In view of Brickner's apparent success with quinine therapy based on inhibition of abnormal lipolytic activity of the serum, it was considered justifiable to repeat previous studies on the lipolytic activity of the serum of patients with multiple sclerosis.

METHOD

The procedure consisted of determining by titration the amount of fatty acid set free from a substrate of neutral olive oil by lipolytic activity of the serum. The technic was similar to that of Crandall and Cherry,[4] with the following modifications: (1) Fiftieth-normal sodium hydroxide was substituted for twentieth-normal sodium hydroxide, to lessen the error in titration, and (2) a better emulsion was obtained when no water was added to the substrate. At least six samples were made up from each serum. Half of them were titrated immediately, to serve as controls, while the remainder were incubated at 40 C. for twenty-four hours prior to titration. The maximum range of experimental error was determined to be 0.4 cc. of fiftieth-normal sodium hydroxide per cubic centimeter of serum, with an average error of 0.1 cc.

RESULTS

Repeated determinations were made over a period of eighteen months on the serums of nine patients with multiple sclerosis. All had clinically typical conditions, which were diagnosed in the department of neurology. In eight patients the colloidal gold curve showed major involvement in the middle tubes, in association with negative serologic reactions of the spinal fluid. In these eight patients all positive variations for lipolytic activity of the serum were within the limits of experimental error. A definite lipolytic activity (1.16 cc. of fiftieth-normal sodium hydroxide per cubic centimeter of serum) was found on one occasion in the serum of the ninth patient but was absent in a later study. This patient was the only one who had not shown clinical evidence of progression of the disease within a year of the determinations. Results of studies made on the serums of sixty-eight dispensary patients without evidence of disease of the central nervous system were negative. This finding is in accord with the work of Crandall and Cherry,[4] although other workers [8] have reported that an olive oil-splitting lipase is frequently present in normal serum. We have found that if normal serum is exposed to air at room temperature for twelve hours prior to incubation, lipolytic activity often

7. Greco, A.: Multiple Sclerosis: Examination of the Cerebrospinal Fluid and Blood Serum and Plasma for Lipase, Note e riv. di psichiat. **64**:1 (Jan.-March) 1935.

8. Comfort, M., and Osterberg, A.: Lipase and Esterase in the Blood Serum: Their Diagnostic Value in Pancreatic Disease, J. Lab. & Clin. Med. **20**:271 (Dec.) 1934.

develops. This development is inconsistent, even with different samples of the same serum, which suggests bacterial contamination as the causative factor. To keep this factor at a minimum, covered sterile glassware and freshly drawn blood were used.

CONCLUSION

In conclusion our studies reveal no substantial evidence to support the concept that abnormal lipolytic activity of the serum is present in multiple sclerosis.

Dr. Merl L. Margason permitted us to study patients with multiple sclerosis who came under his care.

RELATION OF THE HYPOTHALAMUS TO DISORDERS OF PERSONALITY

REPORT OF A CASE

BERNARD J. ALPERS, M.D.
PHILADELPHIA

The obvious approach to the study of personality seems to be psychologic, since most of the attributes of personality appear to be in this field and in the field of the emotions. This statement does not mean, however, that there may not be also a physical basis of the personality and emotions. Attempts to determine what this physical factor consists of have been made in the past with relatively scant success. More recently attention has been directed to changes in personality and mood associated with disease of the hypothalamus. There appears to be both clinical and experimental proof that this region is in some way associated with the regulation of personality and mood and that lesions in this region may cause changes in personality and mood. The case which is reported in this paper appears to throw further light on this problem.

REPORT OF CASE

Diabetes insipidus; marked personality changes; no signs of increased pressure; teratoma of third ventricle; extensive destruction of hypothalamus.

History.—M. B., an attorney aged 39, was referred to the service of Dr. C. H. Frazier by Dr. William G. Spiller on March 26, 1934. He complained of excessive thirst and urination. He was apparently well until July 1932, about twenty months before entrance, when the excessive thirst and urination developed. Several months later he found that he suffered much from the heat but did not perspire a great deal. Following this, headaches developed. Somnolence soon followed; it was so pronounced that he could not remain awake through a meal except with great discomfort. He lost weight, and it was noticed that his entire physical make-up changed. It seemed to his friends as though he were fading away.

Most striking of all were changes in mood and personality. He had always been a mild-mannered person, easy to get along with, tolerant and even tempered, and with a great many friends who were devoted to him. He was not moody but was sensitive.

In April 1933, about one year before the onset of the signs of diabetes insipidus, his wife noticed some peculiarities in his behavior. She noticed, for instance, a tendency on his part to drive his automobile on the left side of the road. He became easily fatigued and very irritable in contrast to his usual buoyant and

---

From the Neurosurgical Clinic and Laboratory of the Hospital of the University of Pennsylvania.

happy self. Normally he had a marked desire for fun and gaiety and an impatience for the morbid or unpleasant. His irritability increased from then on. He was constantly getting into fights with people. He had fist fights with friends. He became hypersensitive and felt that the world was against him. He became incensed with people for inadequate reasons and actually chased people out of his home. He was much more aggressive than usual. He became coarse. He lost all sense of propriety about things. His table manners became bad and his personal appearance less neat. His manner became curt and short in contrast to his great consideration for people normally. He became stubborn and unreasonable. He was so easily fatigued that he slept at odd hours and it was extremely hard to arouse him. These periods alternated with periods of high excitement. At times he was normal both in mood and judgment. One feature noticed by his wife and friends was his decreased tolerance for alcohol. Normally he was able to take a considerable amount without much effect. During the illness a single drink was enough to send him into a rage and to produce complete disorientation. His inability to exert the normal degree of repression and inhibition is illustrated by the fact that he brooked no opposition to his views. Thus, on one occasion when some one who was arguing with him said in response to one of his points, "I don't think so," he flew in a rage and ordered the offender out of his office because he felt that the man had questioned his integrity as a gentleman. He became suspicious of almost every one. One night he went with his wife to visit a friend. On finding that the friend was at work he flew into a rage, accusing him of worshiping money and having no time for friends. He prowled around the house at night, and a few times was found in the cellar. He began to entertain fantastic ideas about all sorts of things. Thus, he had an idea that he could make lots of money by opening a chain of ice cream parlors in Paris.

His judgment both in business and other matters became definitely bad. His judgment in legal matters fell off, and he became careless in handling cases. His brother frequently had to go to court with him because he was afraid the patient would lose his grip on himself and say something that he should not say. One stormy winter day the patient insisted on driving his car to New York. The car skidded and hit a truck; he drove so wildly that his wife insisted on leaving him at Trenton. She continued by train, but he drove the car to New York. His driving in general during the last year of life became very reckless. He drove very fast, weaving in and out among cars.

Among the most striking features of the mental change was severe loss of memory. Memory had been failing for some time, particularly that for recent events. He called clients several times a day about the same matter. He forgot what he had said the moment before. He told the same story over and over. He dictated letters to a stenographer and a half hour later called her back to dictate the same letters over again. One day he asked his wife who she was and denied ever having married her. He would come into his office, close the door, and then stop and ask, "Did I close the door?" He was unable to remember his clients' names or their cases. Toward the end of the illness he was unable to concentrate at all.

The mood showed definite changes. As has been stated, the patient was normally an even-tempered person. During the illness quiet periods alternated with periods of excitement. At parties he made decidedly inappropriate remarks and then laughed at them hysterically. He did silly things. One evening at a party he entered the hostess' closet and dressed up in her clothes. He was unable to understand her displeasure. He did many other silly acts which were not like his usual behavior.

Examination.—Dr. W. G. Spiller found signs of megalomania. The patient said that he was a very fine lawyer, one of the best, and that there was no doubt of it. He said that the government at Washington had asked for his legal opinion. Dr. Spiller stated that without any question on his part the patient volunteered "the information that his estate was worth $100,000."

He was partially disoriented for time and place. He was irritable, argumentative and facetious. There was marked impairment of recent memory.

The right pupil was slightly larger than the left. There was no reaction to light in either pupil. The biceps, triceps, patellar and achilles reflexes were absent

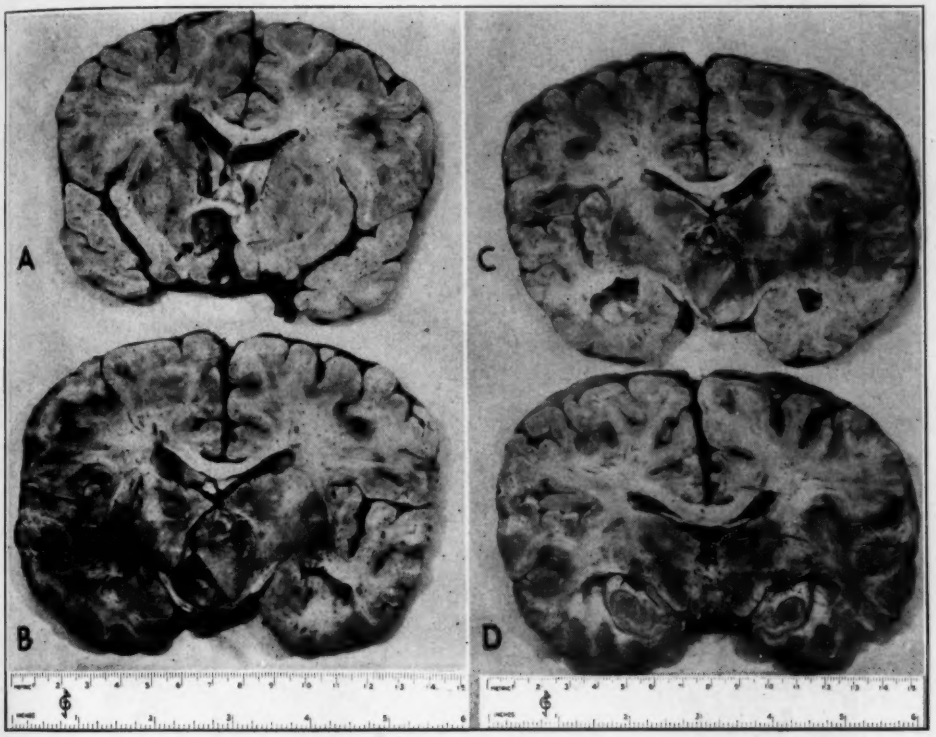


Fig. 1.—The entire extent of the tumor is seen in these photographs. The dermoid extends from the optic chiasm and, to a lesser degree, the preoptic area to the mesencephalon, filling the entire third ventricle. In *A* is seen a slight compression of the preoptic region and left putamen by the wall of the tumor. In *B* and *C* the growth fills the third ventricle and compresses the optic chiasm and hypothalamus. In *D* the cerebral peduncles are seen separated by the posterior wall of the tumor. The mesencephalon was not invaded.

bilaterally. Otherwise neurologic examination gave negative results. There was definite diabetes insipidus.

The Wassermann reaction of the blood was negative. The spinal fluid contained 8 cells. The Wassermann reaction of the spinal fluid was negative; the pressure was 125 mm. of water. There was blurring of the nasal margins of the

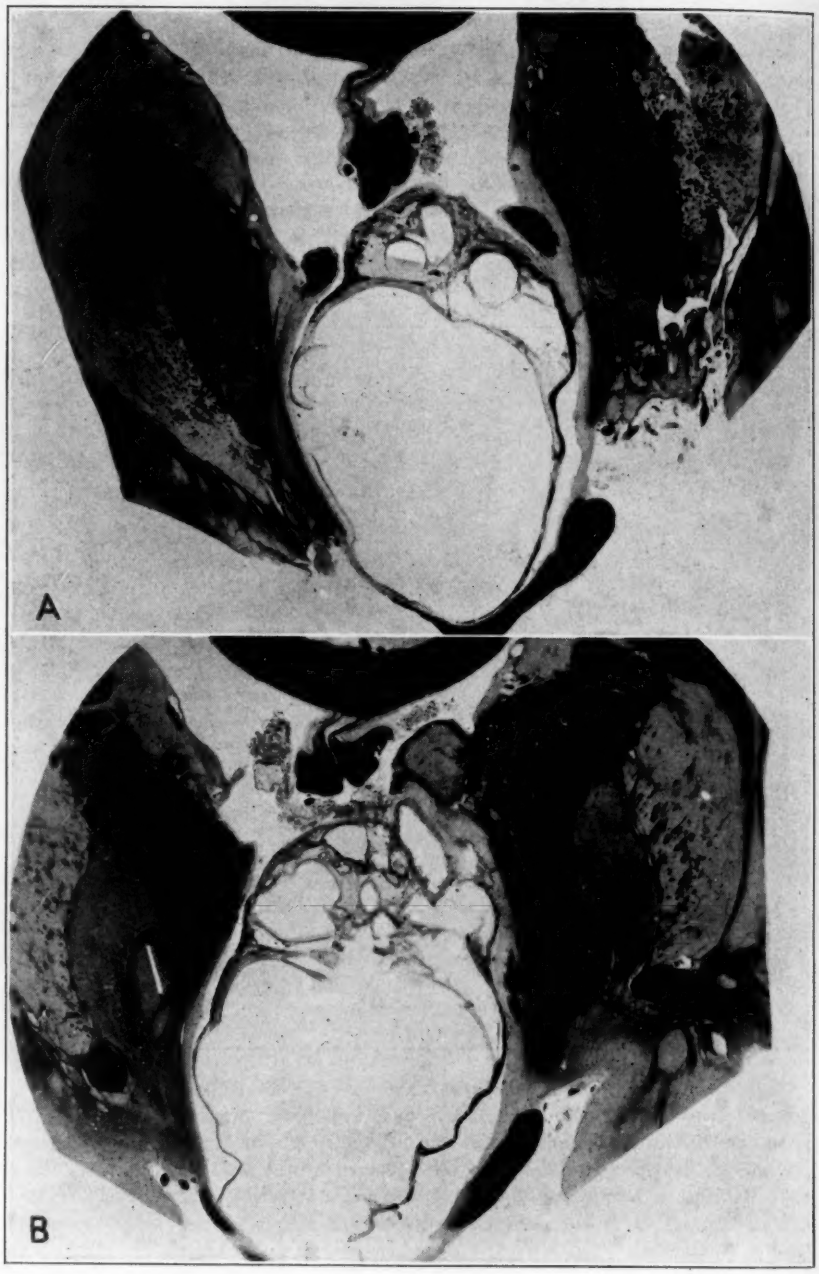


Fig. 2.—*A* shows the tumor at the level of the optic chiasm; Weil stain. It fills the third ventricle, compresses the walls of the ventricle, and distorts and compresses the hypothalamic region. *B* shows the tumor at a more posterior level; Weil stain. Here it causes a marked bellying-out and compression of the structures in the wall of the third ventricle and of the anterior nucleus of the thalamus.

optic disks. The visual fields showed concentric contraction. A roentgenogram of the skull showed multiple sinus disease but no signs of increased intracranial pressure.

An encephalogram revealed that the lateral ventricles were somewhat enlarged. The third ventricle was not seen and appeared to be encroached on. The cisterna chiasmatica was not seen. A diagnosis of a lesion of the third ventricle was made.

Operation.—On April 10, 1934, Dr. C. H. Frazier performed right transfrontal craniotomy but found no tumor in the frontal or suprasellar areas. Death occurred eight days after the operation.

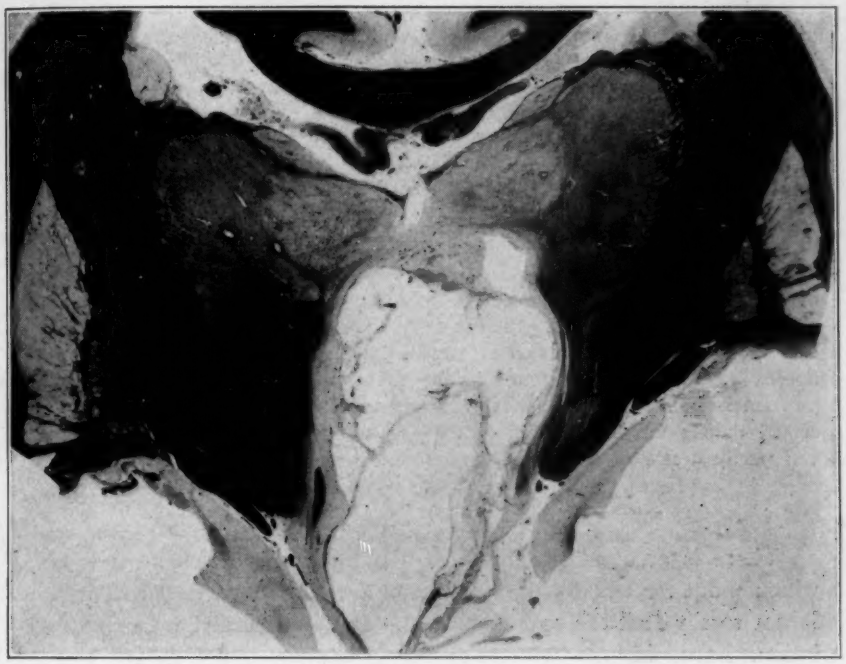


Fig. 3.—In its posterior portion the tumor compresses and invades the medial and lateral thalamic nuclei; Weil stain.

Necropsy.—There was a tumor in the chiasmal and interpeduncular region of the brain. The left optic tract was flattened out and spread over the tumor mass. The corpora mamillaria were pushed posteriorly and greatly displaced. Section of the brain revealed a tumor in the third ventricle, filling the entire cavity. It extended from the anterior commissure to the middle portion of the mesencephalon. It compressed the anterior commissure on the left and the lower portion of the putamen and anterior limb of the internal capsule. The tuber cinereum was greatly thinned. Both optic tracts and the optic chiasm were greatly thinned. The tumor was firmly adherent to the tuber cinereum and to the optic chiasm and tracts. The tumor was encapsulated and could be separated readily from the surrounding structures. It was about half cystic; it measured 2.5 by 3.5 by 2 cm. Histologically the tumor was a teratoma; most of the mass was composed of fat cells. In the more solid portions, however, were large areas of fibrous tissue. Immature glan-

dular structures composed of papillae lined with cuboidal epithelium were present. Immature stratified squamous epithelium was found in a few areas, and cartilage was also present. A portion of the tumor had the typical structure of cholesteatoma.

Histologic Studies.—Serial sections through the entire length of the tumor were made. Alternate sections were stained with hematoxylin-eosin and Weil's modification of the Weigert stain.

Myelin sheath stains revealed that: The thalamus was bilaterally compressed by the tumor in the third ventricle; the nucleus anterior was compressed bilaterally; so too was the nucleus internus (medial nucleus); the nucleus externus (lateral nucleus) was compressed on one side; the rest of the thalamus was not affected. The internal segment of the globus pallidus was compressed bilaterally. The anterior commissure showed complete demyelinization of its middle portion due to compression by the underlying tumor. The columna fornicis of one side was partially demyelinated. Most fibers of the ansa lenticularis were bilaterally compressed and demyelinated. Forel's field was compressed but not demyelinated. The amygdaloid nucleus was bilaterally compressed. From myelin sheath stains it looked as if the entire hypothalamus was destroyed.

Cytologic studies of this region revealed that the substantia grisea was completely destroyed; nothing could be seen of its cells; it had apparently been destroyed by the tumor expanding within the third ventricle. The nucleus supraopticus on one side was completely destroyed, and that on the other side was destroyed except for a small group of cells. The nucleus tuberis lateralis was also destroyed. A few scattered cells remained here and there, but they were not numerous. No cells were found in the nucleus paraventricularis or the nucleus periventricularis. On each side the nucleus tuberomamillaris was fairly well preserved despite the compression of the expanding tumor. The nucleus reuniens was partly destroyed, about half of its cells remaining.

COMMENT

There is accumulating evidence that in the hypothalamus lie areas which influence emotional responses to stimuli of various sorts. This is not to say that the hypothalamus alone is concerned with this regulation. Bard,[1] in an admirable review of the neurohumoral basis of the emotions, called attention to the changes in the emotional responses of dogs and cats after decortication (Goltz, Rothmann, Dusser de Barenne). The evidence for this cortical element will not be reviewed further here; it is mentioned only to emphasize that in the consideration of this problem the hypothalamus is not regarded as the only organic seat for the regulation of the emotions or the personality.

Acute experiments on cats have demonstrated the importance of the hypothalamus as a regulating organ. Thus Bard, employing cats, ablated varying amounts of the brain stem after removing the cerebral cortex. In forty-six successful acute experiments sham rage occurred

1. Bard, P.: The Neuro-Humoral Basis of Emotional Reactions, in Murchison, Carl: Handbook of General Experimental Psychology, Worcester, Mass., Clark University Press, 1934, pp. 264-311.

regularly after ablation of the corpora striata and the rostral half of the diencephalon. Sham rage of maximal intensity occurred when there remained above the midbrain only a thin caudal segment of diencephalon. This consisted of the distal portion of the hypothalamus and a small amount of thalamus, metathalamus and epithalamus. The thalamic portion was shown by other experiments to be unimportant. Bard concluded that "the discharge of nervous impulses which evokes this extraordinary motor activity of the acute decorticate preparation is conditioned by central mechanisms which lie within an area comprising the caudal half of the hypothalamus and the most ventral and most caudal fractions of the corresponding segment of the thalamus."

Further evidence of the importance of the hypothalamic area for the expression of rage is shown by the fact that when this region is released from all cortical control by decortication sham rage is as easily elicited as in transected animals. Thus Bard studied four cats and three dogs which had been decorticated and which survived for long periods. All these animals exhibited definite signs of anger on various stimulations. Their rage differed from the normal in being undirected. Bard concluded that "the pattern of response which constitutes the *expression* of anger in certain mammals depends on a central mechanism that is situated subcortically. The results obtained in acute experiments on cats showed that this neural mechanism is located in the base of the diencephalon. . . . The more recent observation that typical signs of rage can be elicited in dogs and cats during long periods of survival following removal of nearly all cerebral tissue above the hypothalamus supports the earlier findings."

Similar reactions of possibly lesser degree were produced in cats by Fulton and Ingraham.[2] They made incisions into the brains of cats, from 3 to 4 mm. anterior to the optic chiasm, from the midline to the olfactory radiation. The incisions were 2 or 3 mm. deep, were bilateral and were made on the assumption that the frontal lobes give rise to tracts of fibers which pass to centers in the hypothalamus. Rage was produced in three of four cats.

For example, cat 1, an animal "previously friendly and playful, . . . settled into a state of chronic anger aroused to an intense pitch by any friendly advances. Gentle stroking of the animal's back stirred it to a fury of scratching, spitting, and attempting to bite. This condition persisted until the animal was sacrificed five weeks later and both lesions were found to extend to the midline." Cat 2 a few hours after recovery from anesthesia displayed "a marked reaction of rage"

2. Fulton, J. F., and Ingraham, F. D.: Emotional Disturbances Following Experimental Lesions of the Base of the Brain (Pre-Chiasmal), J. Physiol. **67**: xxvii (April) 1929.

which persisted for eleven weeks. A similar reaction was elicited in a third cat but not in a fourth animal. Histologic studies of the brain were not reported. Fulton and Ingraham concluded: "It seems evident to us from gross examination at operation and necropsy that the change of disposition noted in the first three animals was caused by small operative lesions, and that to be effective the lesions must be bilateral. It is probable . . . that cortico-hypothalamic tracts have been divided, thus releasing the hypothalamus and so inducing a state of chronic rage, i. e., a condition in which rage is much more easily elicited than in a normal animal."

Changes in emotional states and in personality have been observed in human beings who had lesions in the hypothalamus (Gagel [3]). Foerster,[4] for example, observed manic reactions while operating on the hypothalamus:

> In one case, while he was operating for a suprasellar craniopharyngioma which compressed the floor of the third ventricle from below, mania developed the moment he began to manipulate the tumor and to produce traction on the hypothalamus. The patient burst forth in a push of speech, quoting passages in Latin, Greek and Hebrew. He exhibited typical sound associations and with every word of the operator broke into a flight of ideas. Thus, on hearing the operator ask for *Tupfer,* he burst into *"Tupfer, Hupfer, Hüpfer, hüpfen sie mal, . . ."* On hearing the word *Messer,* he burst into *"Messer, messer, Metzer. Sie sind ein Metzer, ein Metzel, das ist ja ein Gemetzel, metzeln sie doch nicht so, messen sie doch, sie messen ja nicht, Herr Professor, profiteor, professus sum, profiteri."* These manic responses were dependent on manipulation of the tumor and could be elicited only from the floor of the third ventricle.
>
> In another case, in which Foerster was operating for a papilloma of the choroid plexus, a hemorrhage into the third ventricle resulted from removal of the tumor. When an effort was made to remove the blood clot from the floor of the third ventricle manic excitement followed. The patient had never before exhibited signs of manic tendencies.
>
> In still another case, in which a hypophysial adenoma compressed the hypothalamus, there was a manic reaction with euphoria, lack of insight, push of speech, flight of ideas and motor overactivity, so that the patient could not be kept in bed, ran around the ward in his shirt and interfered with other patients.
>
> In a fourth case a patient with suprasellar tumor who was quiet at the onset of the operation broke into witticisms, made ribald remarks to the nurses and showed flight of ideas as soon as Foerster came to the optic chiasm where the tumor presented. The patient was disoriented and after the operation presented a typical Korsakoff psychosis.

---

3. Gagel, O.: Symptomatology of Diseases of the Hypothalamus, in Bumke, O., and Foerster, O.: Handbuch der Neurologie, Berlin, Julius Springer, 1936, vol. 5, p. 485.

4. Foerster, O., and Gagel, O.: A Case of Ependymal Cyst of the Third Ventricle (A Contribution to the Question of the Relation of Mental Disturbances to the Brain Stem), Ztschr. f. d. ges. Neurol. u. Psychiat. **149**:312, 1933.

Foerster believed that these observations showed that mechanical stimulation of the anterior part of the floor of the third ventricle produces a definite mental syndrome which has all the characteristics of a manic reaction: euphoria, motor restlessness, push of speech and flight of ideas.

Similar manic excitements have been reported by Fulton and Bailey,[5] who asserted that manic attacks occur with tumors at the base of the brain but not with tumors of the hemispheres. They stated: "We ourselves have seen three cases of maniacal excitation after operations for hypophyseal adenoma." They mentioned manic excitement in a case of tumor of the third ventricle reported by Rychlinsky. Fulton and Bailey also stated that Camus noted that dogs with hypothalamic lesions were at first immobile and quiet but later showed sudden crises of agitation, with psychic and motor excitation alternating with periods of profound sleep.

Other cases in point are those reported by Guttmann and Hermann,[6] Schilder and Weissmann,[7] Urechia [8] and Bailey and Murray.[9]

Guttmann and Hermann reported the case of a woman aged 49 who at the age of 27 apparently had had a manic type of psychosis from which she recovered. Later, at 49, another psychosis developed, characterized by attacks of severe anxiety, excitement, irascibility and aggression. Necropsy revealed a tumor in the third ventricle invading the hypothalamus from the chiasm to the corpora mamillaria and spreading up to the fornix and optic tracts. The cortex was not diseased.

The case recorded by Schilder and Weissmann concerned a girl aged 21 who suffered for six months with mental disturbances and amenorrhea. The mental picture was characterized by confusion, loss of memory, disorientation and hallucinations. She heard voices, saw the forms of men and women, and once saw a burning house. She usually saw these before falling asleep. Necropsy revealed a tumor of the hypothalamus, extending from the optic chiasm to the anterior perforated substance, with extension into the third ventricle.

Urechia reported a case of acute mania in a patient with generalized lesions involving all the nuclei in the region of the tuber cinereum and with some enlargement of the hypophysis.

5. Fulton, J. F., and Bailey, P.: Tumors in the Region of the Third Ventricle, J. Nerv. & Ment. Dis. **69**:1 (Jan.); 145 (Feb.); 261 (March) 1929.

6. Guttmann, E., and Hermann, K.: Ueber psychische Störungen bei Hirnstammerkrankungen und das Automatosesyndrom, Ztschr. f. d. ges. Neurol. u. Psychiat. **140**:439 (July) 1932.

7. Schilder, P., and Weissmann, M.: Amente Psychose bei Hypophysengangtumor, Ztschr. f. d. ges. Neurol. u. Psychiat. **110**:767, 1927.

8. Urechia, C. I.: L'examen du système hypophyso-tubérien dans un cas de manie aiguë, Rev. neurol. **1**:585 (April) 1934.

9. Bailey, P., and Murray, H. A.: A Case of Pinealoma with Symptoms Suggestive of Compulsion Neurosis, Arch. Neurol. & Psychiat. **19**:932 (May) 1928.

Bailey and Murray reported a case of compulsion neurosis associated with a tumor of the third ventricle. The patient was a boy aged 15 who at the age of 12 experienced indigestion, constipation, loss of weight and a tendency to vomit. He also drank large quantities of water. Nothing was found on neurologic survey. Since the diabetes insipidus did not respond to posterior pituitary, it was concluded that most of the trouble was neurotic. Investigation from this standpoint revealed evidence of a compulsion neurosis. Under psychotherapy the boy improved so that within a week he was drinking a normal amount of water. Later headache and bitemporal hemianopia developed. He was admitted to a hospital, where he died. Necropsy revealed a large tumor of the third ventricle which extended into both lateral ventricles and connected with a tumor of the pineal gland. The hypothalamus was not studied microscopically.

Psychiatric manifestations associated with the midbrain have been described in a series of contributions by Lhermitte.[10]

In a woman aged 75 there developed suddenly a mesencephalic syndrome characterized by paralysis of both abducens nerves, with headache, vomiting and diplopia. Serologic tests for syphilis were negative. A few weeks later paralysis of the left eye developed with very slight weakness of the lower part of the face on the left side and deviation of the tongue. There was no hemiplegia. One week later the patient began to experience visual hallucinations, which appeared during the day and at nightfall. She saw cats, birds and chickens which made no noise but fixed the patient with their stares. The hallucinations persisted and became so much a part of the patient's experience that she believed implicitly in their existence. No necropsy was performed. Lhermitte postulated a mesencephalic lesion because of the oculomotor paralyses, and assumed that the hallucinations were likewise of mesencephalic origin.

Necropsy was made in a similar case by van Bogaert:[11] The brain of a woman aged 59 who had suffered from oculomotor palsies, hemiplegia and hallucinations of color and animals revealed softening in the cerebral peduncle, red nucleus and lower half of Forel's decussation.

A necropsy was made in another similar case—a case of what Lhermitte calls *l'hallucinose pedonculaire*—by Lhermitte, Levy and Trelles.[12] The patient had suffered acute intoxication from the use of several narcotics. Paralysis of both oculomotor nerves developed, with divergent strabismus of the right eye and crossed diplopia. The pupils were of the Argyll Robertson type. The fundi were normal. A few days after regression of the ocular symptoms there developed dysarthria, mental confusion and hallucinations. For example, at the close of day the patient believed that her room was transformed into a railway or subway car. People entered the car. She talked to them and knew their thoughts. These experiences became less vivid later, but she still found that parts of her room were misidentified and that she saw forms and faces here and there about the room. Necropsy revealed little in the mesencephalon or elsewhere to explain the clinical findings. There were pigmentary degeneration of the reticular gray

10. Lhermitte, J.: Syndrome de la calotte du pédoncule cérébral: Les troubles psychosensoriels dans les lésions du mésencéphale, Rev. neurol. **38**:1359 (Nov.) 1922.

11. van Bogaert, L.: L'hallucinose pédonculaire, Rev. neurol. **1**:608, 1927.

12. Lhermitte, J.; Levy, G., and Trelles, J.: L'hallucinose pédonculaire: Etude anatomique d'un cas, Rev. neurol. **1**:382, 1931.

matter and degeneration of the oculomotor nuclei, but no degeneration was found in the white matter or cortex.

The observations at necropsy in cases of so-called peduncular hallucinations are hardly sufficient to explain the clinical features. The mere coexistence of hallucinations with signs of mesencephalic disease is hardly sufficient evidence that the cause of the hallucinations is in the mesencephalon. This judgment is borne out by the inconclusive nature of the observations at necropsy. The cases are mentioned here because they have been widely cited in the literature as cases of hallucinations due to organic disease of the base of the brain. As stated, the findings hardly warrant this assertion.

Analysis of Evidence.—If one analyzes the laboratory and clinical evidence in cases of hypothalamic injury associated with changes in mood or personality it becomes evident that there are in the hypothalamus areas which under normal circumstances exert an influence on these elements of the human organism. The occurrence of reactions of rage in decorticate cats and dogs indicates clearly that there is a subcortical region which is important for the expression of rage. The ablation experiments of Bard indicate further that this region is in the posterior part of the hypothalamus. As long as this area is intact reactions of rage can be elicited. When it is destroyed they can no longer be obtained. The thalamus proper is not essential for the expression of rage in these animals.

The clinical data are not as definite as the experimental facts, but indicate nevertheless that emotional disturbances may result from lesions in the hypothalamus in the presence of an intact or relatively intact cerebral cortex. Thus, in the case reported the entire group of hypothalamic nuclei were destroyed except for the mamillo-infundibularis group. The cortex was intact. Despite this there were definite changes in mood and personality. The changes in mood were prominent in this case but were not as striking as the deviations of personality. They were manifested by periods of depression, alternating at times with periods of unmotivated excitement, by easily elicited reactions of rage and by loss of inhibitory reactions in general, resulting in uncontrollable laughter or anger. In the cases of Foerster, manic-like reactions were elicited by irritation of the hypothalamus, also in the presence of an intact cerebral cortex. The same statement holds true of the cases of Fulton and Bailey and others. In all respects, the manic excitements which have been elicited by manipulation of the hypothalamic region bear a close resemblance to the manic reactions in manic-depressive psychoses. They differ in that there are usually more involvement of the sensorium and much more confusion. It is better, therefore, in these cases to speak of manic-like reactions rather than

of true manic responses. It seems clear from the clinical cases reported that in man emotional disturbances may occur as the result of either irritative or destructive lesions of the hypothalamus in the presence of an intact cortex.

Changes in personality also may occur, as illustrated clearly in the case reported here. Quantitative intellectual deficits may result. More extensive mention should be made of the changes in personality observed in the case reported, for such changes have not heretofore been observed associated with hypothalamic damage, and in this case they were even more prominent than the changes in mood. As pointed out previously, there is evidence that the changes in personality were profound and severe, that they were at variance with the normal structure of the personality and that they were due neither to an accompanying internal hydrocephalus nor to disease of the cerebral cortex. The specific changes noted were: loss of memory, especially for recent events; loss of inhibitions, with resulting coarseness in action and loss of the niceties of behavior; total lack of appreciation of ordinary courtesies, marked irritability, suspiciousness and hypersensitivity, loss of judgment in business affairs, fits of rage provoked by apparently inadequate stimuli, carelessness in business matters and marked swings of mood from depression to elation. It is clear that there was a severe quantitative reduction in intellectual functions, revealed especially by the loss of memory. This disturbance could not be attributed to the emotional instability, because it was found to be independent of emotional reactions. Its presence in the symptom complex is emphasized because such quantitative intellectual reductions are associated as a rule with the frontal lobe and corpus callosum. There was no evidence of damage to either of these regions.

The mode of action of the various levels in the production of the emotional disturbances and personality changes seems fairly clear. From the results of studies of decorticated and hypothalamic animals it seems proper to assume that the cortex exerts an inhibiting influence on the hypothalamus under normal conditions, so that the expressions of rage or excitement and even of other more refined reactions in man are held normally in check. That this is not the only mechanism involved, however, is shown clearly by the clinical data indicating that manic-like reactions occur in destructive or irritative hypothalamic lesions in the presence of an intact cerebral cortex. This suggests that there is also an inhibitory influence of the hypothalamus on the cortex which is normally present. Possibly there exists a delicate balance between the corticohypothalamic and the hypothalamicocortical stimuli. An interruption at either level produces disturbance in emotional response, and the disturbances at the two levels are quite similar.

SUMMARY AND CONCLUSIONS

A case of dermoid of the third ventricle is reported. The tumor was not associated with hydrocephalus or with signs of increased intracranial pressure.

There were severe changes in personality and in mood, and in neither respect could the changes be attributed to lesions in the cortex or to increased pressure.

Histologic studies revealed severe damage of the nuclei of the hypothalamus, except for the nucleus mamillo-infundibularis. There was much less damage of the thalamus.

Experimental and clinical evidence has been gathered to show that in the hypothalamus are areas damage to which is associated with disturbances in mood. These consist usually of manic-like reactions in the human being and of sham rage in the animal, the latter being elicited when the posterior portion of the hypothalamus is freed from cortical control.

Changes in personality of the type described are unique in hypothalamic symptomatology. No other explanation for their presence was found.

SURVIVAL AND REVIVAL OF NERVE CENTERS FOLLOWING ACUTE ANEMIA

C. HEYMANS, M.D.

J. J. BOUCKAERT, M.D.

F. JOURDAN, M.D.

STANLEY J. G. NOWAK, M.D.

AND

SIDNEY FARBER, M.D.

GHENT, BELGIUM

It is generally accepted that the nerve centers, particularly the bulbar centers, are extremely sensitive to anoxemia, anemia and circulatory disturbances. It has been stated, moreover, that acute anemia or an arrest of circulation not only rapidly depresses but paralyzes the bulbar centers (especially the respiratory center) and that it is impossible to reestablish their functions after the heart has been stopped for more than a few minutes. Although the effects of acute anemia on the nerve centers have been studied by a number of observers,[1] it appears unlikely that arrest of the entire circulation to the nerve centers was achieved by their methods. It has therefore appeared worth while to study this problem again by methods which insure beyond question the cessation of circulation to the nerve centers.

We have attempted to answer the following questions: 1. After what duration of arrest of the circulation do the principal nerve centers lose their functions? 2. After what duration of arrest of the circulation may the nerve centers be revived when the circulation is reestablished?

DURATION OF SURVIVAL

In a first group of experiments,[2] three of us (C. H., F. J., and S. J. G. N.) employed the technic for the perfusion of the isolated head developed by J. F.

From the Institute of J. F. Heymans, the University of Ghent.

1. (*a*) Mayer, S.: Med. Centralbl. **16**:579, 1878. (*b*) Battelli, F.: J. de physiol. et de path. gén. **2**:443, 1900. (*c*) d'Halluin, M.: Presse méd. **12**:345, 1904. (*d*) Pike, F. H.; Guthrie, C. P., and Stewart, G. N.: J. Exper. Med. **10**: 490, 1908. (*e*) Wertheimer, E., and Dubois, C.: Compt. rend. Soc. de biol. **70**:304, 1911. (*f*) de Somer, E., and Heymans, J. F.: J. de physiol. et de path. gén. **14**: 1138, 1912. (*g*) Brukhonenko, S., and Tchetchuline, S.: ibid. **27**:64, 1929.

2. Heymans, C.; Jourdan, F., and Nowak, Stanley J. G.: Compt. rend. Soc. de biol. **117**:470, 1924.

Heymans and his pupils Kochmann and de Somer [3] and adapted to our needs. The completely isolated head of a dog, anesthetized with a compound of chloral and dextrose, was perfused either by a second dog, after the carotid arteries and the jugular veins of the isolated head had been connected with the corresponding vessels of the second dog, or by means of a perfusion pump. The encephalobulbar centers thus isolated and perfused remained alive for many hours. The palpebral, pupillary and motor reflexes were retained. The activity of the respiratory center was manifested externally by the respiratory movements of the larynx and nares.

In a second group of experiments,[2] in which we studied the survival and revival of the pneumogastric, cardioregulatory and vasomotor centers, the perfused isolated head was kept in connection with the trunk by means of the cervical portions of the vagus nerves alone or, in other experiments, by means of the spinal cord alone. Evidence of the activity of the cardioregulatory and vasomotor centers could thus be obtained by observation of the heart rate, the vasomotor tone and the arterial pressure of the trunk. It should be noted that when connections were maintained between the perfused isolated head and the trunk by means of the spinal cord, precautions were taken to prevent circulation to and from the brain by way of the spinal artery and vein. This is a matter of considerable importance in experimental work on the brain of the dog.[4]

When the circulation of the perfused isolated head was interrupted, either by placing clamps on the perfusing vessels or by stopping the artificial perfusion pump, the palpebral, pupillary and motor reflexes disappeared after from three to four minutes of acute anemia. The respiratory, cardioregulatory and vasomotor centers were at first excited and then, after from four to five minutes of arrest of circulation, paralyzed. The encephalobulbar centers, as well as the isolated head as a whole, were than apparently dead.

We may summarize our observations in these two groups of experiments on the survival and revival of the encephalobulbar centers as follows:

1. After an arrest of circulation of from fifteen to twenty minutes, the palpebral and pupillary centers were definitely paralyzed, although the vasomotor and respiratory centers could be revived without difficulty.

2. When circulation to the isolated head was reestablished after an arrest of thirty minutes' duration, the cardioregulatory and vasomotor centers could be revived and could resume their activity.

3. When perfusion was reestablished to the isolated head after an arrest of circulation of thirty minutes' duration, the respiratory center, usually considered to be the center most sensitive to anemia, could be revived and could resume its activity, even after sixty minutes of apparent death.

---

3. Heymans, J. F., and Kochmann, M.: Arch. internat. de pharmacodyn. et de thérap. **13**:379, 1904. De Somer and Heymans.[1f] Heymans, J. F., and Heymans, C.: Arch. internat. de pharmacodyn. et de thérap. **32**:1, 1926.

4. Nowak, Stanley J. G., and Samaan, A.: Arch. internat. de pharmacodyn. et de thérap. **51**:206 (Aug.) 1935.

RESISTANCE TO ACUTE ANEMIA

Resistance to acute anemia of the spinal vasomotor centers was studied with the aid of our modification of the technic for the perfusion of the spleen of a "spinal" dog, B, by a second dog, A.[5] The innervation of the spleen remained intact, but the entire circulation of the spleen was derived from the second dog. Thus, the splenic artery was connected with the carotid artery of dog A, and the splenic vein, with the external jugular vein of dog A. The volume of the spleen of "spinal" dog B, registered by a plethysmograph, was used as an indicator of the activity of its spinal vasomotor centers. Respiration of the "spinal" dog, B, was maintained by artificial means.

When artificial respiration to "spinal" dog B was stopped and circulation to the spinal centers was arrested, the spleen of dog B, still perfused by dog A, began to constrict almost at once. The constriction continued usually for from three to five minutes and was followed by slow, progressive dilatation, usually for twenty-two minutes longer. This group of experiments demonstrated persistence of vasomotor activity in the "spinal" dog for an average of twenty-five minutes after cessation of circulation to the spinal centers.[6]

REVIVAL IN THE INTACT ANIMAL

To complete these observations two of us (C. H. and J. J. B.) studied the revival of the various nerve centers in the intact animal.[7]

In this group of experiments we interrupted the circulation in the anesthetized dog either by asphyxia or by hemorrhage, so that the respiratory, cardioregulatory and vasomotor centers were functionally inactive and the animal appeared to be dead. We then revived the animal, after varying periods of apparent death, by reinjections of blood, intracardiac injections of epinephrine and artificial respiration.

These experiments demonstrated that also in the intact animal the respiratory, cardioregulatory and vasomotor centers can be revived after arrest of circulation for thirty minutes. When the circulation is reestablished, the respiratory and circulatory centers recover their functions; the animal begins to breathe spontaneously, and the circulation returns to normal. The revival of these centers is accompanied by revival of other centers. Dogs thus revived after an arrest of circulation of thirty minutes, however, usually die within from ten to fifteen hours, in a state of narcosis and coma. When the arrest of circulation

5. Heymans, C.: Le sinus carotidien, Rev. belge sc. méd. **1**:507 and 601, 1929. Heymans, C.; Bouckaert, J. J., and Regniers, P.: Le sinus carotidien et la zone homologue cardio-aortique: Physiologie, pharmacologie, pathologie, clinique, Paris, Gaston Doin & Cie, 1933.

6. Farber, Sidney: Preliminary note read at the general meeting of the British Physiological Society, March 14, 1936.

7. Heymans, C., and Bouckaert, J. J.: Compt. rend. Soc. de biol. **119**:324, 1935; Summaries of Communications, Fifteenth International Physiological Congress, 1935, p. 156.

is limited to five minutes or less, there is generally complete recovery of the functions of all centers. When the arrest of circulation lasts more than five minutes, the revived dogs exhibit symptoms probably indicative of lesions [7a] in the cerebrum (narcosis, coma, rigidity and hyperthermia). These regions are apparently much less resistant to anoxemia than the respiratory and circulatory centers. Comparable results have been reported by Winkelbauer.[8] He found that if revival was delayed for more than from five to six minutes (average figures) after apparent death by hemorrhage, the experimental dogs suffered irreparable damage.

CONCLUSIONS

Our experiments demonstrate that the vegetative centers (respiratory and circulatory) possess great resistance to acute anemia nad can be revived even after prolonged arrest of circulation (for as long as thirty minutes). Certain nerve centers, probably situated in the cerebrum and apparently necessary for the continued survival of the organism, are more sensitive to anemia and are irreparably damaged by an arrest of circulation of more than five minutes' duration. Our experiments may throw light on the instances in which patients die several hours or days after revival from apparent death.

3 Albert Baertsoenkaai.

7a. Gildea, E. F., and Cobb, S.: The Effects of Anemia on the Cerebral Cortex of the Cat, Arch. Neurol. & Psychiat. **23**:876 (May) 1931. Andreyev, L. A.: Functional Changes in the Brain of the Dog After Reduction of Cerebral Blood Supply: I. Cerebral Circulation and the Development of Anastomosis After Ligating the Arteries, ibid. **34**:481 (Sept.) 1935; II. Disturbances of Conditioned Reflexes After Ligation of Arteries, ibid. **34**:699 (Oct.) 1935.

8. Winkelbauer, A.: Deutsche Ztschr. f. Chir. **245**:1, 1935.

EFFECT OF EXPERIMENTAL LESIONS OF THE CORTEX ON THE "PSYCHOGALVANIC REFLEX" IN THE CAT

HENRY G. SCHWARTZ, M.D.*
ST. LOUIS

It has been postulated that there are five levels through which autonomic reflexes may be mediated (fig. 1). The accompanying figure illustrates schematically the suggested levels, viz., (*1*) peripheral vascular reflexes having their center in intramural plexuses; (*2*) axon reflexes; (*3*) intrasympathetic reflexes which have their center in the ganglia of the sympathetic trunk; (*4*) medullary and spinal reflexes, and (*5*) cerebral reflexes.

Evidence for the presence of the first level consists almost entirely of the vasomotor phenomena observed by Leriche and Fontaine.[1] It was noted that the blood vessels were not paralyzed after section of the sympathetic as well as the spinal nerves to a limb. The ability of the vessels to contract and dilate on the external application of heat and cold was construed as the basis for the presence of intramural centers in the arterial wall. According to the report, the vasomotor responses could not be interpreted as axon reflexes, since sufficient time elapsed to insure degeneration of the axons.

That autonomic activity may occur by way of the second level (axon reflex) has been sufficiently well established.[2]

The existence of intrasympathetic reflexes (level *3*, fig. 1) affecting glands and viscera was maintained by early investigators.[3] Langley[4]

From the Department of Anatomy, Harvard University Medical School, Boston.

Read before the Boston Society of Neurology and Psychiatry, Dec. 19, 1935.

* This work was begun while the author was a Fellow in Medicine of the National Research Council.

1. Leriche, R., and Fontaine, R.: Experimental and Clinical Contribution to the Question of the Innervation of the Vessels, Surg., Gynec. & Obst. **47**:631, 1928.

2. Bruce, A. N.: Ueber die Beziehung der sensiblen Nervenendigungen zum Entzündungsvorgang, Arch. f. exper. Path. u. Pharmakol. **63**:424, 1910; Vasodilator Axon-Reflexes, Quart. J. Exper. Physiol. **6**:339, 1914. Brady, H.: Ueber Hemmung inflammatorischer Symptome, Skandinav. Arch. f. Physiol. **32**:198, 1915. Krogh, A.: The Anatomy and Physiology of Capillaries, New Haven, Conn., Yale University Press, 1922.

3. Bernard, C.: Du rôle des actions réflexes paralysantes dans le phénomène des sécrétions, J. de l'anat. et physiol. **1**:507, 1864. Sokownin, N.: Bericht über

(Footnotes continued on next page)

and Langley and Anderson [5] disallowed this contention, considering the phenomena to be "pseudo-reflex" in nature. There is evidence, however, that at least one type of true reflex autonomic activity occurs within the sympathetic ganglion. Changes in resistance of the skin in the pad of a cat's forepaw occur in response to reflex activity of the sympathetic nervous system, and a certain fraction of these reflex impulses are mediated solely through the stellate ganglion.[6]

There is adequate proof of the presence of a multiplicity of spinal and bulbar sympathetic mechanisms (level *4*, fig. 1). The inferior ciliospinal center subserving pupillodilatation was described by Budge [7] in 1855 and has long since been confirmed.[8] A reflex center for vasoconstriction,[9] as well as for adrenal secretion,[10] has been localized in the medulla. Brooks has recently presented further evidence of a bulbar [11] and a spinal [12] mechanism which may be normally involved in reflex excitation of the sympathetic system.

---

die physiologischen und histologischen Mitteilungen die auf der 4. Versammlung russischer Naturforscher zu Kasan gemacht wurden, Arch. f. d. ges. Physiol. **8**: 600, 1874; Beiträge zur Physiologie der Entleerung und Zurückhaltung des Harns, Aus dem physiol. Lab. d. Kasaner Universität, Kasaner Universitätsnachrichten, 1877; abstr., Jahresb. ü. d. Fortschr. d. Anat. u. Physiol. (pt. 3) **6**:87, 1878. François-Franck, C. A.: Fonctions réflexes des ganglions du grand sympathique, Arch. de physiol. norm. et path. **6**:717, 1894.

4. Langley, J. N.: On the Physiology of the Salivary Secretion, J. Physiol. **11**:123, 1890; The Sympathetic and Other Related Systems of Nerves, in Schäfer, E. A.: Textbook of Physiology, Edinburgh, Y. J. Pentland, 1900, vol. 2, p. 616.

5. Langley, J. N., and Anderson, H. K.: On Reflex Action from Sympathetic Ganglia, J. Physiol. **16**:410, 1894.

6. Schwartz, H. G.: Reflex Activity Within the Sympathetic Nervous System, Am. J. Physiol. **109**:593, 1934.

7. Budge, J.: Ueber die Bewegung der Iris, Braunschweig, Friederich Vieweg & Son, 1855.

8. Anderson, H. K.: Reflex Pupil-Dilatation by Way of the Cervical Sympathetic Nerve, J. Physiol. **30**:15, 1904.

9. Dittmar, C.: Ueber die Lage des sogenannten Gefässzentrums in der Medulla oblongata, Ber. u. d. Sächs. Gesellsch. d. Wissensch. Math.-phys. Kl. **25**:449, 1873; quoted by Bard.[13c] Owsjannikow, P.: Die tonischen und reflectorischen Centren der Gefässnerven, Arb. a. d. physiol. Anst. zu Leipzig **6**:21, 1871. Ranson, S. W., and Billingsley, P. R.: Vasomotor Reactions from Stimulation of the Floor of the Fourth Ventricle, Am. J. Physiol. **41**:85, 1916. Ranson, S. W.: New Evidence in Favor of a Chief Vaso-Constrictor Center in the Brain, ibid. **42**:1, 1916.

10. Cannon, W. B., and Rapport, D.: Studies on the Conditions of Activity in Endocrine Glands: VII. The Reflex Center for Adrenal Secretion and Its Response to Excitatory and Inhibitory Influences, Am. J. Physiol. **58**:338, 1921.

11. Brooks, C. M.: Delimitation of Central Nervous Mechanism Involved in Reflex Hyperglycemia, Am. J. Physiol. **99**:64, 1931.

12. Brooks, C. M.: Reflex Activation of the Sympathetic System in the Spinal Cat, Am. J. Physiol. **106**:251, 1933.

The fifth, or highest, suggested level of autonomic representation includes both the diencephalon and the cortex. There can be no doubt that the hypothalamus is a sympathetic center.[13] In regard to

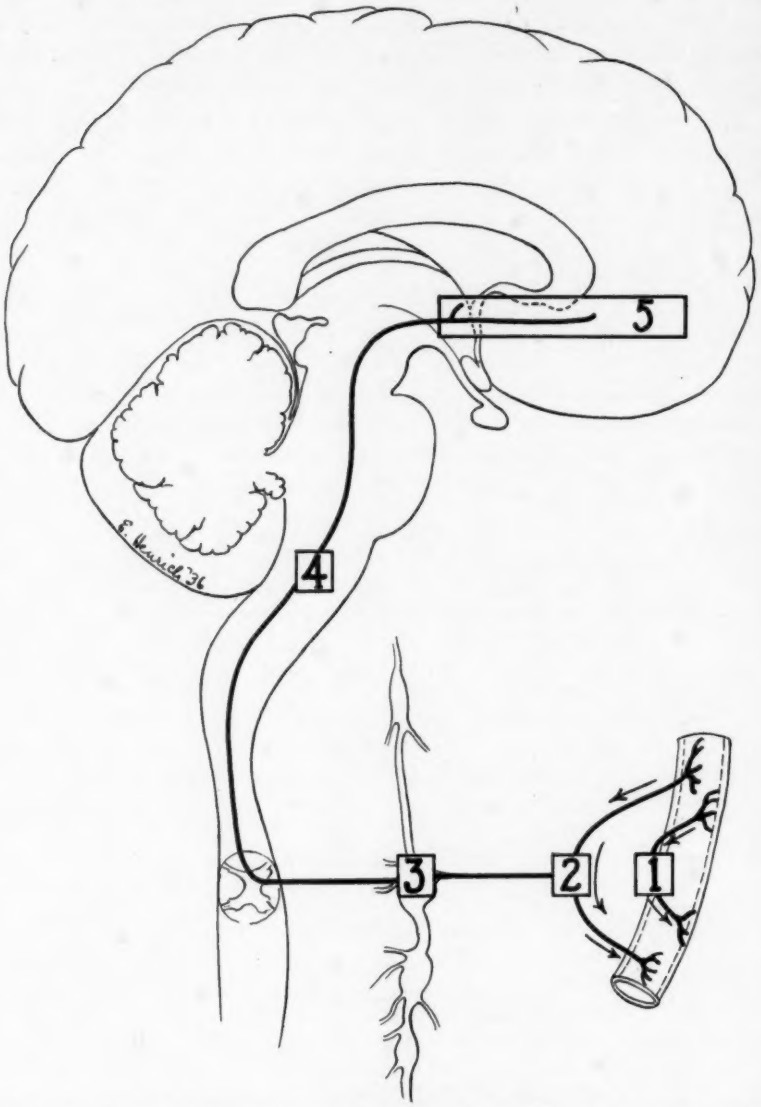


Fig. 1.—Drawing illustrating suggested levels of autonomic reflex activity. Each of the numbers represents a possible reflex center: *1*, intramural; *2*, axonal; *3*, intrasympathetic; *4*, bulbospinal, and *5*, cerebral.

13. (*a*) Goltz, F.: Der Hund ohne Grosshirn, Arch. f. d. ges. Physiol. **51:** 570, 1892. (*b*) Karplus, J. P., and Kreidl, A.: Gehirn und Sympathicus: IV.

(Footnote continued on next page)

cortical localization of autonomic activity, interest for a long time has centered on the region of the frontal lobes.[14]

The present report consists of a series of further investigations on sympathetic mechanisms in the cortex. More specifically, an attempt has been made to determine what effect ablation of various areas of the cortex has on the galvanic response of the skin, i. e., changes in the electrical conductivity of the skin following stimuli which affect the autonomic nervous system. Since this indicator is quite sensitive and can be used to determine quantitatively small, rapid changes in sympathetic activity, it has been applied to the problem. In the course of this investigation, physiologic observations have been correlated with anatomic studies.

METHOD

Unilateral lesions were made in the cerebral cortex of cats. With aseptic technic, intentionally large bone defects were made to obviate any possible sub-

---

ibid. **171**:192, 1918; Gehirn und Sympathicus: VIII. Ueber Beziehungen der Hypothalamuszentren zu Blutdruck und innerer Sekretion, ibid. **215**:667, 1927. (*c*) Bard, P.: A Diencephalic Mechanism for the Expression of Rage with Special Reference to the Sympathetic Nervous System, Am. J. Physiol. **84**:490, 1928; The Central Representation of the Sympathetic System as Indicated by Certain Physiologic Observations, Arch. Neurol. & Psychiat. **22**:230 (Aug.) 1929. (*d*) Ranson, S. W.; Kabat, H., and Magoun, H. W.: Autonomic Responses to Electrical Stimulation of Hypothalamus, Preoptic Region, and Septum, ibid. **33**: 467 (March) 1935.

14. (*a*) Eulenburg, A., and Landois, L.: Ueber die thermischen Wirkungen experimenteller Eingriffe am Nervensystem und ihre Beziehung zu den Gefässnerven, Virchows Arch. f. path. Anat. **68**:245, 1876. (b) François-Franck, C. A.: Leçons sur les fonctions motrices du cerveau (réactions voluntaires et organiques) et sur l'épilepsie cérébrale, Paris, Octave Doin, 1877. (*c*) Parsons, J. H.: Notes on Ophthalmic Neurology: Dilatation of the Pupil from Stimulation of the Cortex Cerebri, J. Physiol. **26**:366, 1901. (*d*) Bechterew, W.: Der Einfluss der Hirnrinde auf die Thränen-, Schweiss- und Harnabsonderung, Arch. f. Physiol., 1905, p. 297. (*e*) Winkler, F.: Die zerebrale Beeinflussung der Schweiss-sekretion, Arch. f. d. ges. Physiol. **125**:584, 1908. (*f*) Langworthy, O. R., and Richter, C. P.: The Influence of Efferent Cerebral Pathways upon the Sympathetic Nervous System, Brain **53**:178, 1930. (*g*) Brickner, R. M.: Certain Characteristics of the Cortical Influence over the Sympathetic Nervous System in Man, J. Nerv. & Ment. Dis. **71**:689, 1930. (*h*) Fulton, J. F.: Forced Grasping and Groping in Relation to the Syndrome of the Premotor Area, Arch. Neurol. & Psychiat. **31**:221 (Feb.) 1934. (*i*) Kennard, M. A.; Viets, H. R., and Fulton, J. F.: The Syndrome of the Premotor Cortex in Man: Impairment of Skilled Movements, Forced Grasping, Spasticity, and Vasomotor Disturbance, Brain **57**:69, 1934. (*j*) Pinkston, J. O.; Bard, P., and Rioch, D. McK.: The Responses to Changes in Environmental Temperature After Removal of Portions of the Forebrain, Am. J. Physiol. **109**:515, 1934. (*k*) Bucy, P. C.: Frontal Lobe of Primates: Relation of Cyto-Architecture to Functional Activity, Arch. Neurol. & Psychiat. **33**:546 (March) 1935. (*l*) Kennard, M. A.: Vasomotor Disturbances Resulting from Cortical Lesions, ibid. **33**:537 (March) 1935.

sequent effects of altered intracranial pressure or cerebral herniation. In cases in which the most anterior portion of the frontal pole was to be excised, the frontal sinus was opened and its superior and posterior walls were rongeured away. The sinus itself was then sponged with tincture of iodine and plugged with wax. After this procedure had been carried out, these instruments were discarded in favor of freshly sterilized ones, and the dura was opened to approach the brain itself. Various portions of the cerebral cortex were removed, as will be set forth in the individual descriptions of the groups of experiments. In completing the operation, care was taken to suture the dura; this step successfully minimized the number of cortical adhesions.

After recovery, the animals were studied at regular intervals for from three to six months after the operation. Changes in the electrical conductivity of the skin were measured by the apparatus which has been previously described.[6] Briefly, the technic consisted of applying nonpolarizable electrodes of zinc and zinc sulfate to the pad of the forepaw and the ear. The skin of the ear had previously been pricked, with the result that practically all the resistance of the cat existed in the skin of the pad. The electrodes were then connected in parallel with a known resistance, through which a known direct current, measured by a microammeter, was passing. The change in the ammeter reading thus was inversely proportional to the resistance of the cat, which could be easily calculated. Since the reflexes following cerebral ablation in the present investigation were either normal or absent, the absolute time relations, latent period, duration, etc., were not studied.

Readings were taken from both forepaws. Several types of stimuli capable of producing changes in the resistance of the skin were applied: (1) pressure over the forelimbs; (2) pinching the tail or the middle of the back, and (3) whistling or tapping the nose. At the end of the experiments the brains were removed, and the lesions were checked histologically (Nissl technic) in serial sections.

RESULTS

In figure 2 are shown frontal and sagittal views of the cat's brain. The cruciate sulcus is clearly seen, surrounded by the posterior and anterior sigmoid gyri. In subdividing this area the symbols of Langworthy[15] are used. Areas A, B, C, E and F are electrically responsive. Stimulation of areas A and B gives contraction of the contralateral foreleg; stimulation of area C gives movement of the facial and masticatory musculature of the opposite side; no response can be elicited from area D, and stimulation of areas E and F controls the contralateral hindleg. Langworthy has shown that area D has the cytologic characteristics of a sensory area. Areas B, C E and F are histologically motor, containing a definite gigantopyramidal layer. Area A, however, although electrically responsive, is histologically characteristic of the area frontalis agranularis (area 6) of Brodmann, as determined in cats by Winkler and Potter,[16] and marks the transition between the

15. Langworthy, O. R.: The Area Frontalis of the Cerebral Cortex of the Cat: Its Minute Structure and Physiological Evidence of Its Control of the Postural Reflex, Bull. Johns Hopkins Hosp. **42**:20, 1928.

16. Winkler, C., and Potter, A.: An Anatomical Guide to Experimental Researches on the Rabbit's Brain, Amsterdam, W. Versluys, 1914.

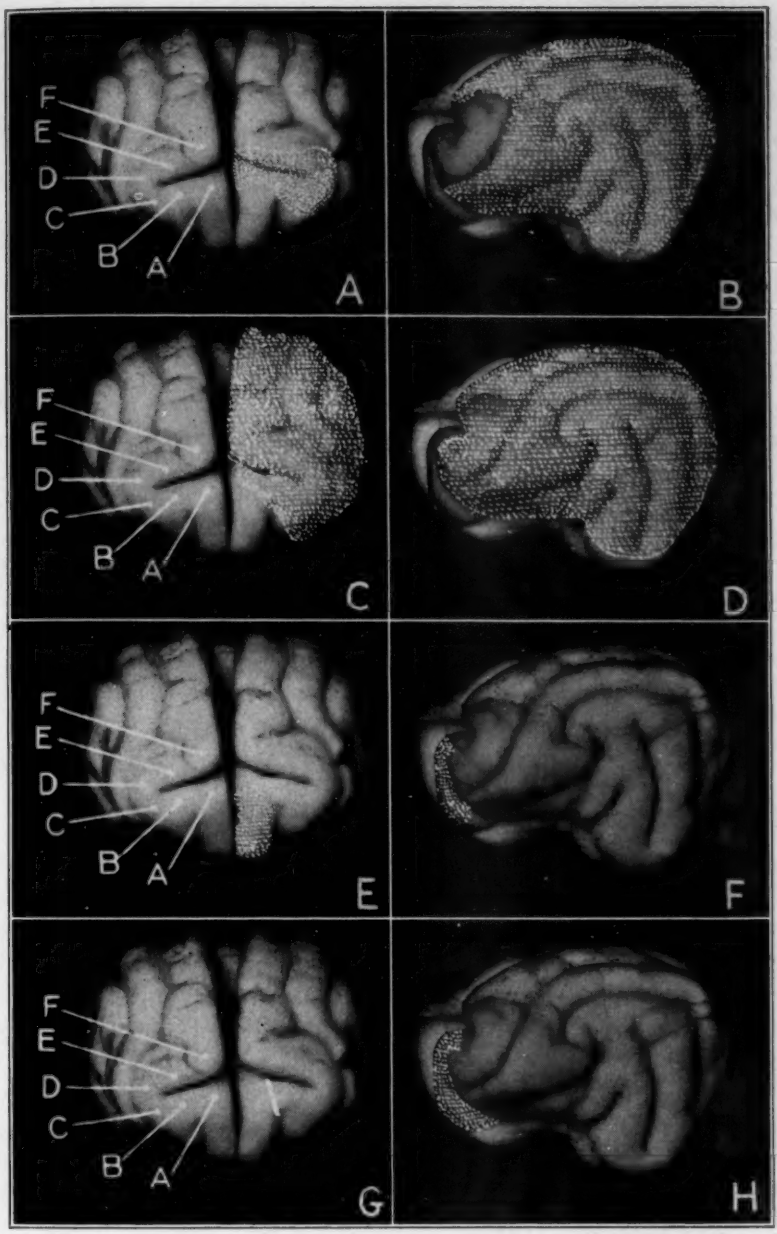


Fig. 2.—Frontal and sagittal views of the cat's brain. The anterior and posterior sigmoid gyri are subdivided according to Langworthy.[15] Area 6 (Brodmann) includes subdivision A and extends anteriorly and ventrally over the upper third of the adjoining gyrus proreus. Stippling indicates the extent of the cortical excisions: *A*, in cat G-4; *B*, in cat G-7; *C* and *D*, in cat G-10; *E* and *F*, in cats R-1 and S-3, and *H*, in cat S-2. The white line in *G* indicates the cortical incision between areas 4 and 6 in cat G-8.

motor area and the area frontalis agranularis. Langworthy preferred to speak of this region as the intermediate motor area, or the area frontalis. The area extends from the edge of the sulcus cruciatus forward and downward, through the upper third of the gyrus proreus (appearing in the photographs as the most anterior gyrus). The lower two thirds of the gyrus proreus are relatively undifferentiated cortex.

I. *Observations Following Unilateral Excision of the Sensorimotor Area.*—The stippled area in figure 2 *A* indicates the extent of a lesion of the left anterior and posterior sigmoid gyri, as determined histologically. Areas A and B were absent; almost all of areas C, D, E and F were removed. The excised area thus included a small part of the area frontalis agranularis (area A), as well as the electrically responsive cortex. The greater part of the area frontalis was preserved. Normal responses were obtained in both forelimbs (fig. 3). On pinching the tail, tapping the nose or whistling, a fall in the resistance of the skin resulted. Similarly, pressure on one forelimb caused a response in both it and its partner of the opposite side. From the work of Brooks [12] and Schwartz,[6] it appears that the stimulus in the last instance need not reach the higher levels; the reflex arc may be confined to the spinal cord or the stellate ganglion, thus being segmental in type. The responses shown by this animal (G-4) were in no way different from those in a normal cat.

II. *Observations Following Extensive Unilateral Excision of the Cortex Posterior to the Sensorimotor Area.*—(*a*) The lesion in this case (G-7) extended laterally on the left side from the sulcus splenialis (on the medial surface of the cortex) to the pyriform lobe. Posteriorly, the cortex was removed from the posterior border of the sensorimotor area through the gyrus suprasylvius posterior, at the occipital pole. The gyrus fornicatus, the head of the nucleus caudatus, the amygdala and the hippocampus were intact. Despite the extensive lesion (fig. 2 *B*), normal changes in cutaneous resistance persisted on both sides (fig. 3).

(*b*) Another animal was subjected to a similar operation. This lesion differed slightly from that in the preceding experiment. A small part of area F was included. Laterally, the cortex was removed from the sulcus splenialis to the posterior rhinal sulcus. Posteriorly, the lesion extended to the gyrus splenialis posterior, sparing the extreme tip of the occipital pole. The fornix, claustrum, caudate nucleus, globus pallidus and most of the pyriform lobe were intact. The amygdala was injured posterolaterally. The thalamus was normal except for retrograde degeneration. Normal measurable responses to appropriate stimuli occurred on both sides in this animal (G-9).

III. *Observations Following Unilateral Removal of the Cortex Posterior to Area 6.*—The medial part of area A and the entire gyrus proreus were preserved on the left side in this experiment (animal G-10; fig. 2, *C* and *D*). The cortex was removed posteriorly as far as the tip of the occipital pole, and laterally from the gyrus fornicatus to the hippocampus. The caudate nucleus, globus pallidus, putamen and amygdala were spared. Figure 3 illustrates normal changes in the resistance of the skin on both sides.

IV. *Observations Following Lesions of the Left Area Frontalis Agranularis.*—Figure 2 *H* illustrates the extent of the lesion suffered

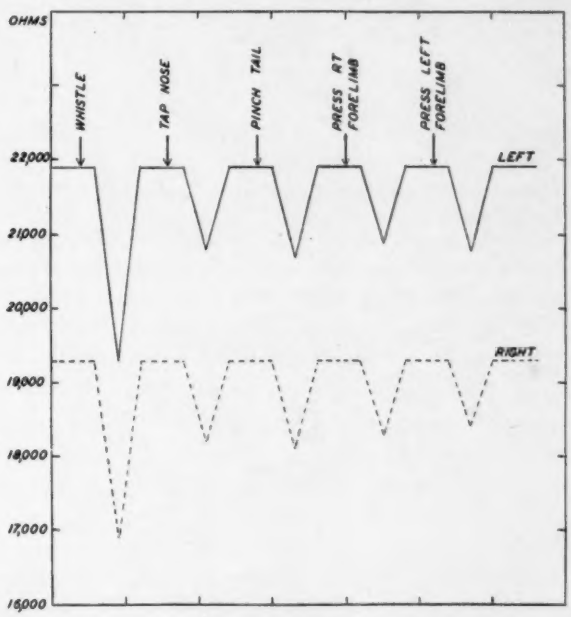


Fig. 3.—Responses obtained in cat G-10, after excision of the cortex posterior to area 6 on the left side. Both segmental galvanic reflexes (response to pressure over the forelimb) and psychogalvanic reflexes (on whistling or tapping the nose) appeared on both sides, as in normal animals, on which no operation had been performed. The same responses were obtained after excision of the left sensorimotor area (cat G-4), after unilateral ablation of the cortex posterior to the sensorimotor area (cats G-7 and G-9) and after cortical incision between areas 4 and 6 (cat G-8). In this figure and in subsequent figures, the ordinates indicate the measured resistance. The abscissas represent approximately the relative time relations for each response; no attempt was made to measure exactly the absolute time relations or the latent period.

by cat S-2, the effects of which are represented in fig. 4. Only a small caudal portion of the transitional area A was preserved; the remainder, with the gyrus proreus, was excised. Areas B and C were cytologically

intact. Normal responses were obtained on the left, that is, in the limb ipsilateral to the lesion. Changes in resistance in response to pressure over the forelimb occurred on both sides, i. e., a segmental

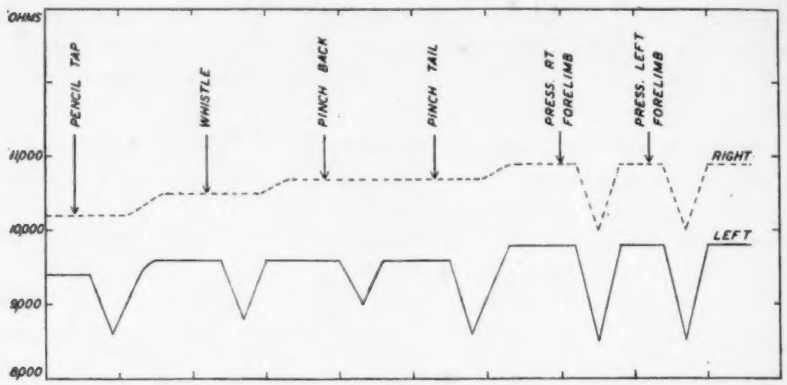


Fig. 4.—Typical responses obtained in cat S-2, after excision of the left area frontalis agranularis and the gyrus proreus. Normal reflex changes in response to all stimuli occurred on the left (ipsilateral) side. On the right (contralateral) side segmental galvanic reflexes persisted, but psychogalvanic responses and the response to pinching the tail or middle of the back were abolished.

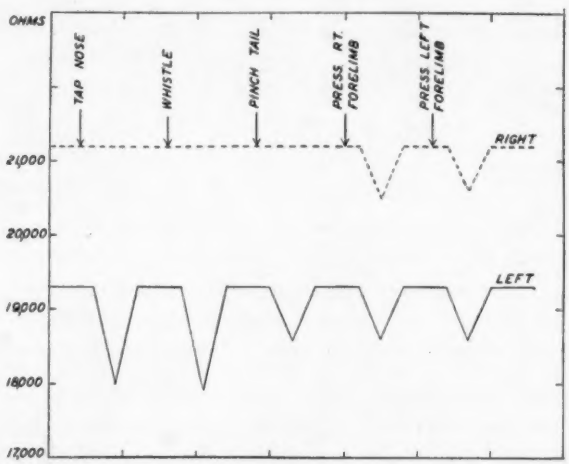


Fig. 5.—Observations on cat R-1, after excision of area 6 on the left. Psychogalvanic responses and the response to pinching the tail or the back were abolished on the contralateral side. Similar results were obtained in cat S-3 after the same cortical lesion.

reflex. The response to more general stimuli which elicit an "emotional" reaction (tapping on the table with a pencil or a sudden whistle), i. e., a psychogalvanic reflex, was not obtained on the right side, contralateral

to the lesion, nor was any measurable change observed after pinching the back or the tail.

Similar effects were observed in animals (S-3 and R-1) with slightly less extensive lesions of the left area frontalis (fig. 2 *E* and *F*). The psychogalvanic reflex was absent on the contralateral side (fig. 5).

V. *Observations Following a Discrete Incision Between Areas 4 and 6.*—In order to rule out the possible influence of any intracortical connections between areas 4 and 6, an incision was made as pictured (fig. 2 *G*) at the transition between area A and area B. Sections showed a fine scar through the cortex at the point described. There was a decrease in the number of large pyramidal cells in area A, but otherwise no degeneration. Normal responses were obtained on both sides (fig. 3).

COMMENT

I. *Localization of the Cortical Area Influencing the Psychogalvanic Response.*—From the results described, it is clear that in the cat the integrity of the psychogalvanic reflex depends on the presence of the area frontalis agranularis (area 6 of Brodmann). Figures 4 and 5 indicate that excision of this area is followed by absence of the response to "psychic stimuli" (i. e., stimuli producing an emotional reaction) on the side contralateral to the lesion. In animals in which area 6 was preserved, normal responses were obtained.

Since the galvanic response of the skin is a manifestation of autonomic nervous activity [17] and since in the recent literature various autonomic phenomena have been localized in the frontal lobe of higher mammals, subhuman primates and man, the discrete localization of the psychogalvanic response resulting from the present group of experiments was not unexpected. It is apparent that the results agree with the early experiments of von Bechterew and Winkler. Using no general anesthesia, von Bechterew [14d] found that stimulation of the medial portion of the anterior segment of the gyrus sigmoideus anterior in cats resulted in marked sweating of the footpads, especially on the contralateral side. Undercutting or excision of the area was followed by greatly diminished sweating contralaterally. Winkler [14e] confirmed the localization of the area by stimulation but observed no difference on the two sides; his experiments were performed under light narcosis

17. Schilf, E., and Schuberth, A.: Ueber das sogenannte psychogalvanische Reflexphänomen beim Frosch und seine Beziehung zum vegetativen Nervensystem, Arch. f. d. ges. Physiol. **195**:75, 1922. Gildemeister, M.: Der galvanische Hautreflex als Teilerscheinung eines allgemeinen autonomen Reflexes, ibid. **197**:432, 1922. Minor, L.: Ueber erhöhten elektrischen Hautwiderstand bei traumatischen Affektionen des Halssympathicus, Ztschr. f. d. ges. Neurol. u. Psychiat. **85**:482, 1923.

induced with ether or ethyl carbamate. In subhuman primates, it has been variously reported that destruction of the premotor area (area 6) is followed by increased sweating on the opposite side [14h] or diminution in the secretion of sweat.[14i]

Langworthy and Richter [14f] demonstrated galvanic responses of the skin in etherized cats after stimulation of either one of two cortical areas of the intact brain. Changes in electrical conductivity of the skin occurred in all four limbs, more marked, however, on the side contralateral to the electrically stimulated cortical region. A greater response was obtained from area 6 (area A plus the upper third of the gyrus proreus, fig. 2) than from a region just posterolateral to the motor area. No responses were obtained after stimulation of any other portions of the cortex.

II. *Terminology.*—In this report an attempt has been made to distinguish between the "psychogalvanic" reflex, on the one hand, and the "segmental" type, on the other (page 316). The latter, as has been shown, can occur independently of the cortex; the reflex arc may be confined to the spinal cord, without the stimulus rising to higher centers.

Unpublished observations in this laboratory have repeatedly shown the absence of a psychogalvanic reflex in completely decorticate cats. The psychogalvanic reflex, therefore, depends on a cortical mechanism. According to this conception, if the term "psychogalvanic" is used, it should refer to the following chain of events: A peripheral stimulus reaches the higher association levels (area 6 in cats), where, for want of a better term, "an emotional reaction" is elaborated; the impulse then passes downward to the brain stem and the spinal cord, where sympathetic responses are effected. In the present group of experiments, the external signs of strong "emotion" were observed after a loud whistle or tapping the nose. The cat blinked its eyes and attempted to either withdraw or attack; the pupils became slightly dilated. In short, the cat presented a picture which one has learned to associate with fear or rage.

That such a distinction between "segmental galvanic" and "psychogalvanic" reflexes should be applied not only to reflexes involving resistance of the skin but to pilomotor responses is suggested by the work of Brickner.[14g] In two well studied cases of hemiplegia he referred to two types of pilomotor reactions. One is the "simple pilomotor reflex," mediated "through a simple reflex arc, segmentally and without the involvement of any long ascending or descending tracts within the central nervous system." The other is the "pilomotor response to an emotional stimulus." Brickner showed that the latter response occurred intensely on the hemiplegic side but was rarely, if

ever, present on the unaffected side. The reaction noted in response to an emotional stimulus was considered by Brickner to be due probably to a pyramidal lesion. The responsible neuron probably arises "in some part of the cortex, and, traversing the capsule in company with the pyramidal fibers, must pass to some lower part, probably of the diencephalon, there to act upon what have come to be known as the sympathetic nervous centers."

III. *Nature of the Cortical Control.*—Cortical somatic motor control has been regarded as chiefly inhibitory,[18] and Bard [13c] suggested that the production of sham rage in cats might be explained on the basis of a "release phenomenon." Whether the cortical area involved plays an inhibitory or an excitatory rôle in autonomic activity is still open to question.[14l] According to the observations of Pinkston, Bard and Rioch,[14j] chronic vasodilatation occurs in dogs and cats after removal of the contralateral sensorimotor area. This may be interpreted as being due to removal of a dominant vasoconstrictor mechanism.

From their observations on changes in the resistance of the skin, Langworthy and Richter [14f] concluded that cerebral control of preganglionic sympathetic fibers is predominantly inhibitory. This may be true so far as segmental galvanic reflexes of the skin are concerned. However, on the basis of their own experiments, in which stimulation of area 6 caused a fall in resistance, and from the results reported in this paper, it is more probable that the cortex acts in an excitatory rôle in eliciting the psychogalvanic response in cats.

IV. *Lack of Response to Pinching the Tail or the Back After Excision of Area 6.*—It is difficult to explain the lack of response on the side contralateral to the lesion after a painful stimulus is applied to the tail or the middle of the back. There are two possibilities. First, the stimulus may travel up long ascending paths to the cortex by way of the thalamus. Since removal of the premotor area results in abolition of the contralateral cutaneous response, it would be necessary to postulate that the efferent pathway passes from the cortex directly downward and across to the autonomic cells of the spinal cord. Interruption of this efferent neuron by cortical excision would abolish the reflex. The manifest objection to this interpretation lies in the fact that, in all probability, connections, either direct or indirect, between the sensory fibers and the final autonomic preganglionic efferent pathway exist at lower levels—in the spinal cord, the medulla or the thalamus.

---

18. Jackson, J. H.: Evolution and Dissolution of the Nervous System, Brit. M. J. **1**:591, 660 and 703, 1884. Head, H.: Release of Function in the Nervous System, Proc. Roy. Soc., London, s.B **92**:184, 1921.

A second possibility is that there is some cerebral dominance over intersegmental reflexes. To be accepted, this supposition would necessitate a further postulate, namely, that after removal of the higher centers, an unknown mechanism makes the lower centers inaccessible to afferent impulses coming in from other segments.

SUMMARY AND CONCLUSIONS

1. The observations reported were made on cats which were allowed to live for from three to six months after operative procedures on the cortex.

2. Changes in resistance of the skin in response to adequate stimuli were measured repeatedly during the postoperative period, after which the animals were killed and their brains studied histologically.

3. It is concluded that the integrity of the major portion of area 6 (premotor area, or area frontalis agranularis) is necessary for the production of a psychogalvanic response. Furthermore, the mechanism involved is a crossed one.

4. From the observations reported, it is considered probable that the intact area 6 is an excitatory center involved in the psychogalvanic reflex.

5. A distinction has been made between "psychogalvanic" and "segmental galvanic" reflexes. Segmental responses occur apparently independently of cortical control.

6. It is possible that there is some cerebral dominance over intersegmental reflexes.

THE CEREBRAL CIRCULATION

XXXI. EFFECT OF ALCOHOL ON CEREBRAL VESSELS

CAROLINE BEDELL THOMAS, M.D.*

BOSTON

The changes in circulation following the use of alcohol are probably more universally recognized than those produced by any other drug. Nevertheless, the circulatory effect of alcohol in the body is difficult to analyze, because it is the resultant of a number of direct and reflex effects both on the heart and on the blood vessels in different vascular areas. In order to evaluate properly the action of alcohol on a given vascular bed, such as the cerebral circulation, it is desirable to review briefly the facts already known about its circulatory effects.

There is general agreement that large doses of alcohol [1] administered intravenously produce an abrupt fall in blood pressure with cardiac slowing or standstill, followed by rapid recovery (Dixon [2] decerebrate cats, dogs and rabbits; Brooks,[3] unanesthetized dogs and Hyatt,[4] unanesthetized dogs with transections of the lower thoracic portion of the cord). Neither fall in pressure nor cardiac retardation occurs if both vagus nerves are cut. Intravenous injection of moderate doses [5] produces no change in the heart rate (Dixon, men and animals, and Hyatt, dogs prepared as already described) and either no change (Brooks, Hyatt) or a slight rise (Dixon) in blood pressure. Hyatt injected 40 per cent alcohol continuously at a rate of 2 cc. per minute and found no effect on blood pressure for from twenty-five to seventy-five minutes; thereafter the arterial pressure fell rapidly, and death ensued.

Large doses of alcohol [6] given by gastric fistula or stomach tube

---

From the Department of Neuropathology, the Harvard University Medical School.

* Medical Fellow of the National Research Council.

1. Such as 10 cc. of 25 per cent alcohol per dog.

2. Dixon, W. E.: The Action of Alcohol on the Circulation, J. Physiol. **35**:346, 1906-1907.

3. Brooks, C.: The Action of Alcohol on the Normal Intact Unanesthetized Animal, J. A. M. A. **55**:372 (July 30) 1910.

4. Hyatt, E. G.: The Action of Alcohol on the Heart and Respiration, J. Lab. & Clin. Med. **5**:56, 1919-1920.

5. Such as 5 cc. of from 5 to 40 per cent alcohol per dog.

6. Such as from 0.5 to 5 cc. of from 10 to 90 per cent alcohol per kilogram for cats or 16 cc. of 40 per cent alcohol per dog.

produce no immediate effect on the blood pressure or the heart rate (Brooks, unanesthetized dogs; Lieb,[7] decerebrate cats, and Hyatt, dogs). Brooks found that after fifteen minutes the arterial pressure began to fall, with decrease in the amplitude and increase in the rate of the heart beat for an hour or more.

When concentrated alcohol was administered by mouth, the investigators aforementioned all noted quickening of the heart rate and immediate rise in arterial pressure, lasting five or ten minutes. This effect was ascribed to the irritant action of alcohol on the mucous membranes of the mouth, initiating a cardio-accelerator reflex, and so was not considered a specific pharmacologic action. The transient rise in pressure and pulse rate after the ingestion of alcohol noted by Grollman[8] in men who were nondrinkers may well have been due to this irritant action rather than to a "psychic response," as he described it, and its infrequent occurrence in moderate drinkers may be attributed to acquired tolerance of the mucosa. Sulzer,[9] using a Starling heart-lung preparation, corroborated the absence of cardiac stimulation by alcohol in any dose. He found that impairment of the functional capacity of the heart began when the concentration of alcohol in the blood reached 0.06 per cent and increased with increasing concentrations. Above 0.1 per cent there were progressive constriction of and reduction of flow in the coronary arteries. Above 0.3 per cent a rise in venous and pulmonary arterial pressures appeared. In the intact animal, however, McDowall[10] observed a different effect: After intravenous injection of 2 cc. of 50 per cent alcohol into a cat weighing from 2 to 3 Kg., a marked fall in venous pressure occurred, while the arterial pressure was maintained. The fall in venous pressure he ascribed to dilatation of the capillaries of the skin. That such dilatation may occur without change in blood pressure he considered to be an indication of the redistribution of blood and its partial withdrawal from vital organs. This bears out Dixon's[2] plethysmographic studies, in which he showed that injection of alcohol in the intact animal dilates the vessels of the skin rapidly, while constricting the arteries supplying muscular and splanchnic areas. When mammalian arteries from different areas are isolated, however, they respond uniformly to perfusion

7. Lieb, C. C.: The Reflex Effects of Alcohol on the Circulation, J. A. M. A. **64**:898 (March 13) 1915.

8. Grollman, A.: The Action of Alcohol, Caffeine, and Tobacco on the Cardiac Output (and Its Related Functions) of Normal Man, J. Pharmacol. & Exper. Therap. **39**:313, 1930.

9. Sulzer, R.: The Influence of Alcohol on the Isolated Mammalian Heart, Heart **11**:141, 1924.

10. McDowall, R. J. S.: The Action of Alcohol on the Circulation, J. Pharmacol. & Exper. Therap. **25**:289, 1925.

with alcohol. Thus, isolated arteries perfused with from 0.1 to 0.2 per cent alcohol dilated slightly, whereas perfusion with from 1 to 2 per cent alcohol produced considerable constriction, followed later by dilatation. It is likely, therefore, that the difference in the behavior of vessels in the skin and that of vessels in splanchnic areas in the intact animal depends on vasomotor reflexes.

After the work of Hill [11] in 1896, it was widely assumed that the cerebral circulation is entirely dependent on the level of general arterial pressure in the body. According to this conception, a rise in general pressure brings about passive dilatation of cerebral arteries and increased cerebral circulation, while a fall in pressure leads to diminished blood supply to the brain and the arterial walls, deprived of their distending force, contract passively. Among the scattered reports which throw doubt on this theory are two describing the effect of alcohol. Hirschfelder [12] and Berezin [13] in abbreviated reports described independently the dilatation of exposed cerebral vessels after the administration of alcohol, but no attempt was made to preserve normal relationships in intracranial pressure.

In 1928 Forbes [14] devised a method of making direct measurements of the caliber of pial arteries through a tight window in the skull which maintained intracranial dynamics in a normal state. He and his associates have shown the pial arteries to be independently reactive to a variety of mechanical, chemical and reflex stimuli. The present study was undertaken in the same laboratory to determine the effect of alcohol on the caliber of pial arteries.

METHOD [15]

Cats were anesthetized with dial. The animal's head was immobilized in a clamp, and after the dura mater had been removed, a metal-rimmed window was screwed into a trephine hole in the left parietal region. The air beneath the window was driven out and replaced with cerebrospinal fluid. A microscope with a micrometer eyepiece was focused on the field. Arterial pressure was recorded from the femoral artery, and cerebrospinal fluid pressure, from the cisterna magna. Artificial respiration was given throughout the experiments. The surface of the brain was examined immediately, and a suitable pial artery, measuring from 100

11. Hill, L.: The Physiology and Pathology of the Cerebral Circulation, London, J. & A. Churchill, 1896.

12. Hirschfelder, A. D.: Effect of Drugs upon Vessels of Pia Mater and Retina, J. Pharmacol. & Exper. Therap. **6**:597, 1915.

13. Berezin, V. I.: Action of Poisons on the Vessels of the Brain, Russk. Vrach **15**:513, 1915; abstr., J. A. M. A. **67**:844 (Sept. 9) 1916.

14. Forbes, H. S.: The Cerebral Circulation: I. Observation and Measurement of Pial Vessels, Arch. Neurol. & Psychiat. **19**:751 (May) 1928.

15. Details of the technic employed are described fully in Forbes' original paper.[14]

to 200 microns in diameter, was selected. Its caliber was measured at intervals of from one-half to ten minutes. The magnification of the microscope was usually 80. The finest division of the micrometer scale was equivalent to 7 microns, and the smallest change in arterial caliber which could be measured precisely was 3.5 microns, or half of one division on the scale. A preliminary base line was established during which the artery showed no change in diameter greater than 3.5 microns for from ten to twenty minutes. Readings of the arterial and cisternal pressures were recorded by an assistant. A similar method was employed in several experiments on rabbits.

The dilutions of alcohol used were freshly made of chemically pure ethyl alcohol in Ringer's solution (in the first five experiments freshly distilled water was the diluent). Injections were made into the saphenous vein and the carotid artery; the alcohol was also administered by stomach tube and applied locally beneath the window.

During several experiments photomicrographs of pial vessels were taken. Two experiments were performed with the assistance of Dr. Frederick A. Gibbs and

TABLE 1.—*Relationship of the Dose and Speed of Intravenous Injection of Alcohol to the Degree of Arterial Change*

Degree of Arterial Change, Percentage			Number of Trials	Average Dose, Cc. per Kg.	Average Length of Period of Injection, Min.	Average Dose Injected per Minute, Cc. per Kg. per Min.
Constriction	Medium	7-18	10	1.25	2.1	0.60
	Small	2- 6	11	1.08	2.2	0.49
	None	0	11	1.12	2.1	0.53
Dilatation	Great	27-47	9	1.13	1.3	0.87
	Medium	11-18	12	1.20	2.55	0.47
	Small	4- 7	7	1.03	2.40	0.43
	None	0	3	1.20	2.5	0.48

Erna B. Gibbs in which measurements of cerebral blood flow were obtained from the right parietal lobe with Gibbs'[16] thermo-electric flow recorder, while a pial artery in the corresponding part of the left parietal lobe was observed in the usual way.

RESULTS

1. *Intravenous Injection of Alcohol in Anesthetized Cats.*—The greatest number of experiments were performed in this group: Thirty-four injections of 25 per cent alcohol were carried out in fifteen cats.

Dosage: All doses are expressed in terms of cubic centimeters of absolute alcohol per kilogram of body weight. The average dose was 1.1 cc. per kilogram. In twenty-four trials the dose was from 1 to 1.3 cc. per kilogram, in the remaining ten trials the dose falling within the limits of 0.75 and 1.6 cc. per kilogram. The rate of injection varied from 0.25 to 2 cc. per kilogram per minute. As will be shown later, variations both in the total dose and in the speed of injection had important bearing on the physiologic effects observed (table 1).

16. Gibbs, F. A.: A Thermoelectric Blood Flow Recorder in the Form of a Needle, Proc. Soc. Exper. Biol. & Med. **31**:141, 1933.

Caliber of the Pial Artery: Intravenous injection of 25 per cent alcohol was followed by a characteristic series of changes in arterial caliber in thirty-one trials.[17]

Injection of alcohol usually initiated prompt slight arterial constriction followed by pronounced and rapid dilatation, with subsequent slow return to the original caliber. Dilatation was the more constant and striking feature of this biphasic reaction (figs. 1 and 2). Constriction was noted in twenty trials, or 64.5 per cent of the series (figs. 3 and 5 *A*); in three of these instances constriction occurred in the absence of subsequent dilatation. Dilatation was produced in every one of the fifteen cats, and in twenty-eight trials in which dilatation occurred there was no preceding phase of constriction.

The initial constriction began while the alcohol was still being injected and reached an average maximum of 7.1 per cent of the artery's original diameter in one minute and twenty-five seconds.[18] Without a pause, the phase of dilatation ensued, reaching a peak in an average of four minutes and ten seconds, when

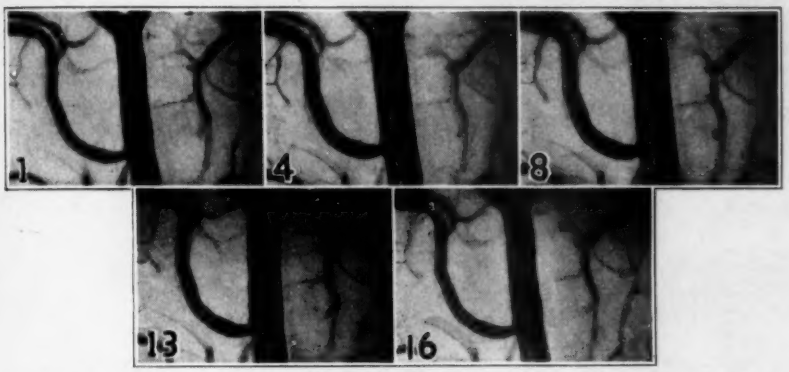


Fig. 1.—Dilatation of a pial artery after intravenous injection of alcohol. Five of a series of sixteen photomicrographs (actual magnification, × 80) are shown (cat 2; trial 2). Alcohol was injected between 3:38 and 3:39½ p. m. In the legend for this figure and in that for figure 3, A.D. indicates the arterial diameter, expressed in microns.

1: 3:37 p. m.; A.D., 154 microns; control.
4: 3:41 p. m.; A.D., 197 microns; artery dilating.
8: 3:43½ p. m.; A.D., 210 microns; peak of 35 per cent dilatation.
13: 3:49 p. m.; A.D., 175 microns; artery constricting.
16: 3:56 p. m.; A.D., 161 microns; diameter almost back to normal.

17. In two of the remaining three trials the smallest doses were given (0.75 and 0.8 cc. per kilogram); since there was no response of the artery, the stimulus may be considered to have been subliminal. In the third trial the artery constricted 13 per cent of its diameter in eleven and one-half minutes and remained so for over an hour. The solution of alcohol was discarded and a fresh one prepared: the artery responded characteristically in two subsequent injections. This atypical trial seemed, therefore, technically questionable, and the results were not included in the averages.

18. All time intervals were calculated from the beginning of the injection.

the average arterial diameter was 19.5 per cent greater than before the injection. Maximal dilatation was maintained for less than thirty seconds; in only one instance did the artery remain fully dilated for over a minute. The return to the

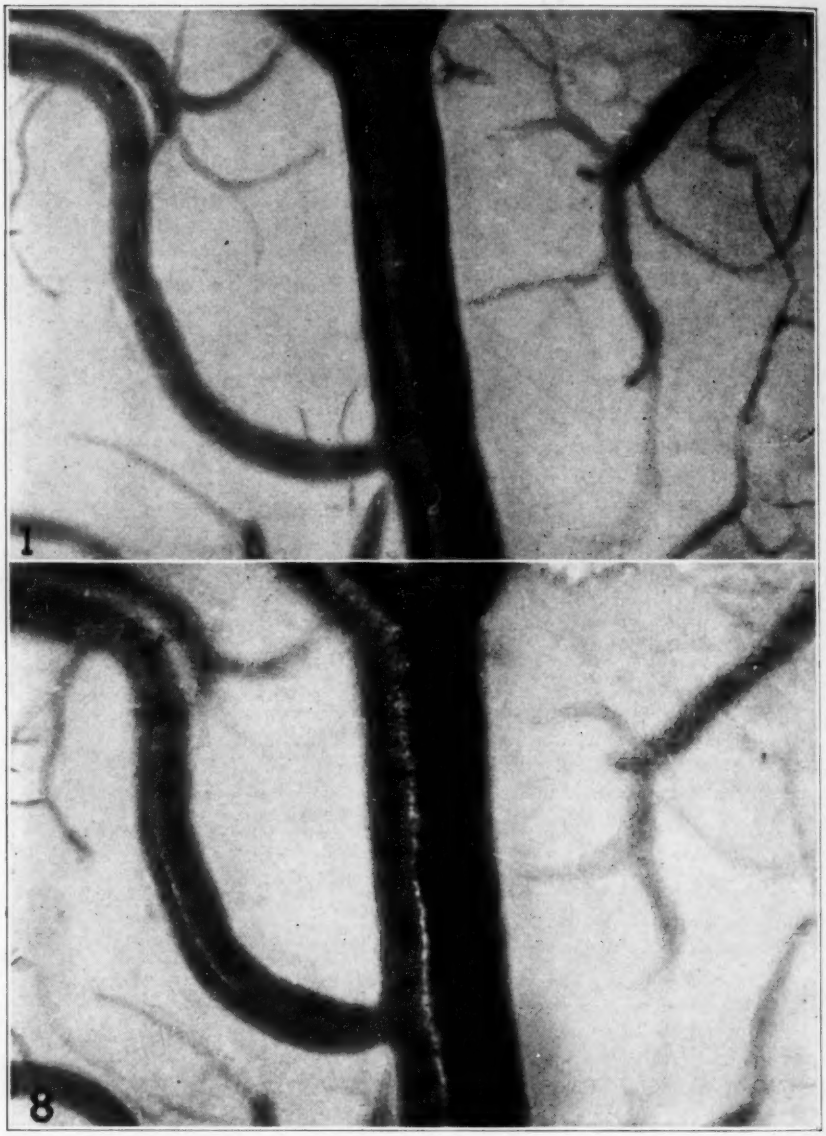


Fig. 2.—Enlargements of photomicrographs shown in figure 1, showing dilatation of the pial artery after intravenous injection of alcohol. *1* was taken before the injection of alcohol, and *8*, at the peak of the 35 per cent dilatation.

normal caliber was slow and of variable length, taking from five to twenty minutes in the majority of trials, with an average of fifteen minutes. In three instances

the artery returned to normal in less than five minutes, and in two instances it took more than twenty minutes. The caliber of the resting artery at the end of the trial had returned to the original base line in one third of the experiments, while in one-third it was slightly greater than the initial diameter (from 3 to 5 per cent) and in one-third a little less.

In the eleven trials in which dilatation alone occurred and in the three trials in which characteristic constriction alone took place, the time relationships showed them to be expressions of the usual cycle of constriction and dilatation already described, even though one or the other phase was absent (table 2).

Appearance of the Pial Veins: Whenever dilatation of the pial artery was pronounced, the color of the pial veins changed from blue to red, and the flow of blood in the veins became visibly faster. This was usually associated with a fall

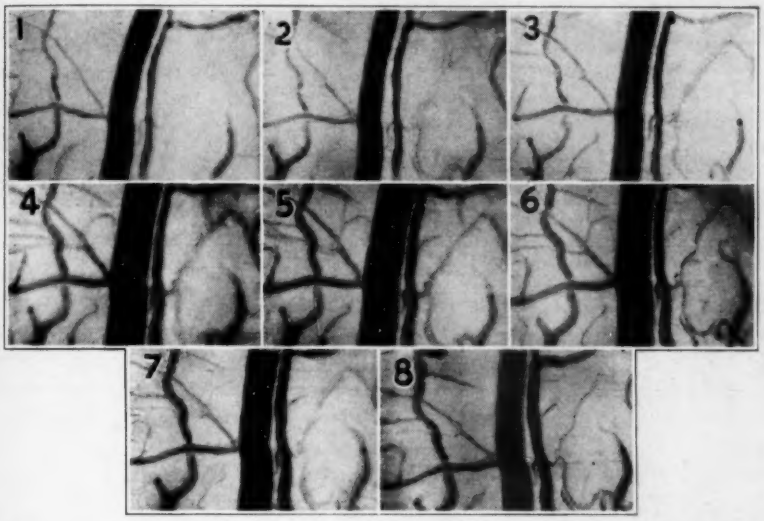


Fig. 3.—A series of eight photomicrographs (actual magnification, ×80), showing slight constriction and subsequent rapid dilatation of a pial artery following intravenous injection of alcohol (cat 7; trial 2). Note the red corpuscles in the vessels shown in exposure *3*. When *3* was taken, the arterial pressure had fallen from 112 to 16 mm. of mercury, and the blood flow had momentarily ceased. Alcohol was injected between 2:46½ and 2:48½ p. m.

1: 2:46 p. m.; A.D., 158 microns; control.
2: 2:47½ p. m.; A.D., 154 microns; slight constriction; blood flow slowed.
3: 2:49 p. m.; A.D., 164.5 microns; artery dilating; blood flow stopped.
4: 2:49¾ p. m.; A.D., 196 microns; artery dilating; blood flow normal.
5: 2:50½ p. m.; A.D., 217 microns; peak of dilatation.
6: 2:51¾ p. m.; A.D., 203 microns; artery constricting.
7: 3 p. m.; A.D., 179 microns; artery constricting.
8: 3:20 p. m.; A.D., 160 microns; diameter back to normal.

in arterial pressure and occurred during the time when arterial pressure was lowest, during the latter part of the dilatation. The veins did not show any significant change in caliber.

Cisternal Pressure: After the injection of alcohol the cerebrospinal fluid pressure always rose promptly, reaching an average height of 64 mm. of water above the basal level in two minutes and thirty-six seconds, remaining there for thirty seconds and returning to normal in ten minutes and fifty-four seconds. The pressure never fell below the initial level and always described a single, simple curve. Even in the two trials in which the dose was so small that the pial artery was unaffected, the cisternal pressure rose 10 and 12 mm. of water, respectively.

TABLE 2.—*Effect of Intravenous Injection of Alcohol on the Caliber of the Pial Artery*

Reaction of Pial Artery		Number of Trials	Average Change in Arterial Caliber, Percentage	Length of Time After Injection That Maximum Change in Caliber Occurred	
				Min.	Sec.
Constriction	Followed by dilatation	17	7.1	1	20
	Not followed by dilatation	3	6.9	1	56
	Total	20	7.07	1	25
Dilatation	Preceded by constriction	17	18.4	4	10
	Not preceded by constriction	11	21.3	4	20
	Total	28	19.5	4	14

TABLE 3.—*Response of Arterial Pressure to Intravenous Injection of Alcohol and Its Correlation with the Dose, Speed of Injection, Cisternal Pressure and Changes in Caliber of the Pial Artery*

Group	Response of Arterial Pressure	Number of Trials	Average Dose, Cc. per Kg.	Average Length of Period of Injection, Min.	Average Change in Cisternal Pressure, Mm. of Water	Average Change in Arterial Pressure, Mm. of Mercury	Arterial Constriction		Arterial Dilatation		
							No. of Trials in Which Constriction Was Present	Average in Effective Trials, Percentage	No. of Trials in Which Dilatation Was Present	Average in Effective Trials, Percentage	Time of Peak of Dilatation, Min.
I	No change	4	1.20	3.2	+26.0	0	2	4.0	4	9.0	3.9
II	Rise	12	1.22	2.8	+34.4	+21.5	9	7.0	9	11.3	4.7
III	Fall	6	1.15	1.6	+68.7	—39	5	8.3	6	19.1	3.3
IV	First fall, then rise	9	1.04	1.3	+126.7	—52, then +27	4	5.2	9	32.8	4.5

Arterial Pressure: Unlike the cerebrospinal fluid pressure, the arterial blood pressure presented four types of response (table 3). In four trials there was no change in arterial pressure following the injection of alcohol (fig. 4 *D*); in twelve trials (not including the two in which subliminal doses were used) the arterial pressure rose (fig. 4 *A*), reaching an average peak of 21.5 mm. of mercury above the original level in two minutes and fifty seconds. In six trials the arterial pressure fell (fig. 4 *B*) an average of 39 mm. of mercury in two minutes and eleven seconds, and in nine trials the pressure first fell 52 mm. of mercury in one

minute and forty-eight seconds and immediately rose, reaching a peak of 27 mm. of mercury above the original base line in four minutes and forty-two seconds and then returned to normal (fig. 4 *C*).

The sharp fall in blood pressure noted in the last two groups was usually accompanied by cardiac arrhythmia. Extrasystoles, varying degrees of heart block

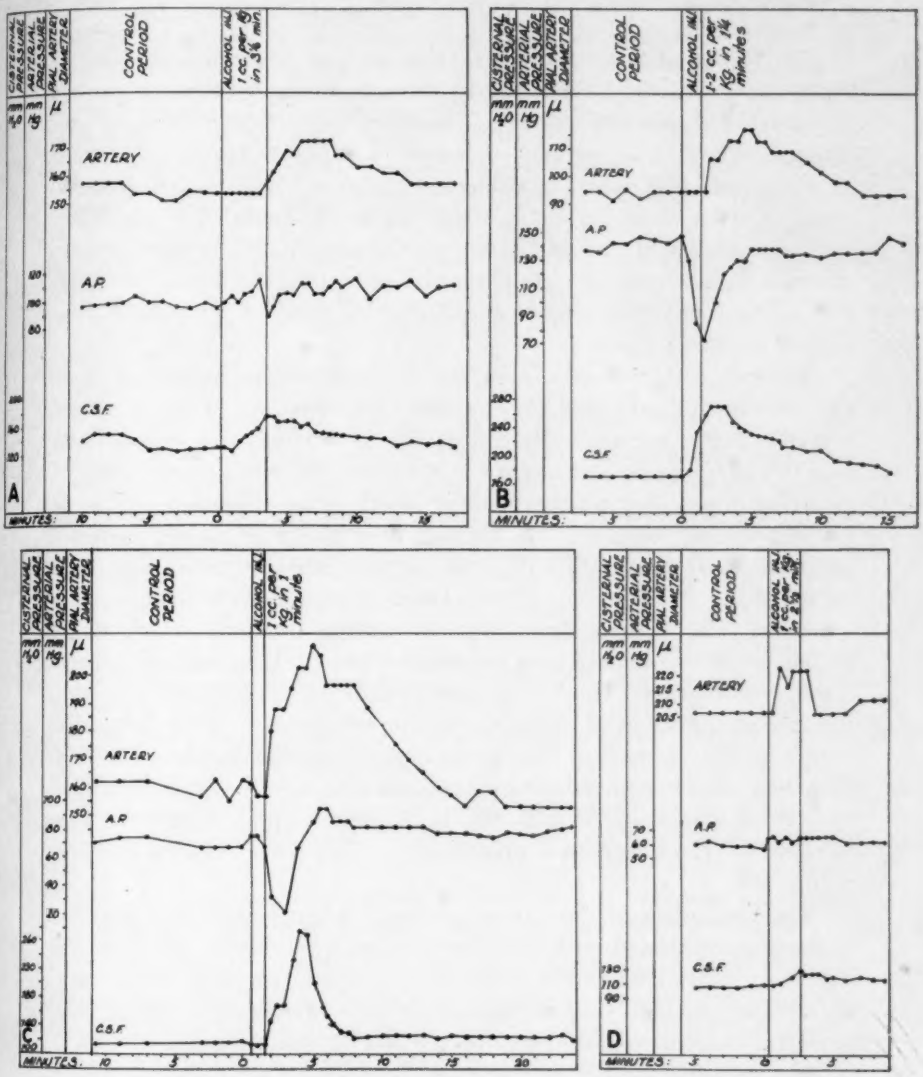


Fig. 4.—Dilatation of the pial artery in response to intravenous injection of alcohol, showing its independence of changes in arterial pressure. *A* (cat 8, trial 2) shows arterial dilatation associated with a slight rise in arterial pressure (group II); *B* (cat 4, trial 2), dilatation associated with a sharp fall in arterial pressure (group III); *C* (cat 2, trial 1), dilatation associated with a sharp fall and a subsequent rise in arterial pressure, and *D* (cat 14, trial 2), dilatation associated with unchanged arterial pressure.

and complete ventricular asystole, lasting a number of seconds, were observed. During the period of asystole the blood pressure fell rapidly, in some instances nearly to zero, before ventricular contraction was renewed. In one case electrocardiographic records taken after the injection of 1.2 cc. of absolute alcohol per kilogram of body weight showed marked exaggeration of the T waves and dropped beats when the arterial pressure was at its lowest.

Correlation of Arterial Caliber, Dose, Rate of Injection and Cisternal and Arterial Pressures: The factors determining the presence or absence of constriction are not clear. As shown in table 1, there was no significant difference in the dose or speed of injection between the trials in which constriction was of moderate degree and those in which it was small or even absent. Nor was the degree of constriction dependent on the direction of change of the arterial pressure. The average constriction in the trials in which arterial pressure rose was 7 per cent, and in those in which arterial pressure fell it was 8.3 per cent—almost exactly the same (table 3).

The concentration of alcohol in the blood stream depends both on the quantity injected and on the speed of injection. Table 1 shows that the degree of dilatation was closely correlated with the quantity injected per minute rather than with either the dose or the rate of injection alone. For all the trials in which great dilatation (from 27 to 47 per cent) occurred, the average dose was 0.87 cc. per kilogram per minute, as compared with 0.43 cc. when the dilatation was small (from 4 to 7 per cent). Such large effective doses were usually associated also with a sharp drop in arterial pressure, which might or might not be followed by a secondary rise of pressure above normal. Table 3 demonstrates conclusively that dilatation of pial vessels following intravenous injection of alcohol is not merely passive. First, dilatation occurs in the absence of change in general arterial pressure; second, dilatation occurs both when the pressure rises and when it falls, and finally, the magnitude of dilatation is correlated with the effective dose of alcohol. The dilatation is greater when a sharp fall in blood pressure occurs.

The magnitude of the rise of cisternal cerebrospinal fluid pressure is likewise correlated with the dose injected per minute and with the degree of dilatation. In the three trials in which dilatation was absent, the arterial pressure rose 36, 16 and 18 mm. of mercury, respectively, while the cisternal pressure rose 36, 10 and 32 mm. of water.

Controls: This group of experiments was controlled in two ways. First, careful observation of the diameter of the pial artery before every injection of alcohol demonstrated the absence of spontaneous fluctuations of any magnitude capable of being confused with the experimental results. Second, Ringer's solution was injected intravenously into several cats, the volume and rate of speed being equivalent to those used when alcohol was given. In no instance was there any

change in the caliber of the pial artery, although minor fluctuations in cisternal pressure and, more rarely, in arterial pressure were noted.

Simultaneous Observation of the Cerebral Blood Flow and the Diameter of the Pial Artery After Intravenous Injection of Alcohol: In two anesthetized cats a Gibbs' flow recorder was introduced into the parietal lobe opposite the cranial window through a small trephine hole fitted with a bone button. Simultaneous records of the blood flow, the diameter of the pial artery and the pressure in the femoral artery were obtained after the intravenous injection of alcohol. In three trials the dilatation measured 38.8, 44 and 33 per cent, respectively; systemic arterial pressure was practically unchanged in the second trial but fell sharply in the other two. In all three trials the blood flow in the

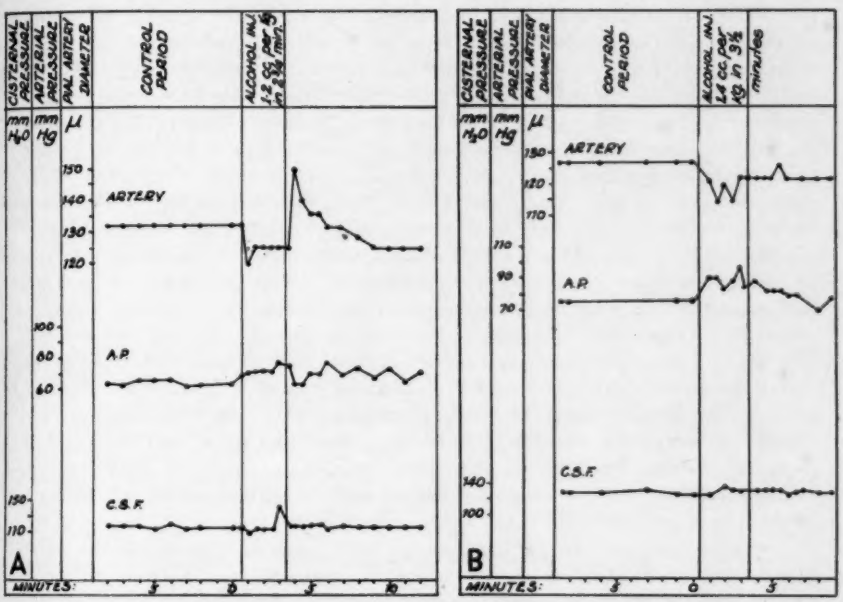


Fig. 5.—Constriction of the pial artery following intravenous injection of alcohol. *A* (cat 10, trial 2) shows arterial constriction followed by dilatation and *B* (cat 10, trial 3), arterial constriction without subsequent dilatation.

parietal lobe was diminished during the early part of the phase of dilatation but increased rapidly to more than normal as the dilatation reached its peak.

2. *Intracarotid Injection of Alcohol in Anesthetized Cats.*—A series of thirteen injections of 10 and 25 per cent alcohol was carried out on four cats, in which the solutions were injected into the left carotid artery. (The cranial window was always on the left side).

Dosage: The average dose was much smaller than in the series of intravenous injections—0.17 cc., as compared with 1.1 cc. of absolute alcohol per kilogram. In all but two injections in the intracarotid series the dose was either 0.15 or 0.2 cc. In eight trials the alcohol was diluted to 10 per cent; in five trials, to 25 per cent. In nine trials the solution was injected rapidly, in from

eight to eighteen seconds (average, twelve and three-tenths seconds), while in four trials the alcohol was injected more slowly, in from twenty-five to forty seconds (average, thirty-one and three-tenths seconds). The rate of injection varied from 0.3 to 1.5 cc. per kilogram per minute; interestingly, this is the range of the rates of injection in the intravenous series, (from 0.25 to 2 cc. per kilogram per minute).

Caliber of the Pial Artery: Within ten seconds of the beginning of injection the artery usually became colorless and empty of blood corpuscles; it then constricted rapidly and immediately began to dilate. The constriction occurred too rapidly to be measured. Marked dilatation occurred in twelve of the thirteen trials; in the thirteenth there was a mere flicker, amounting to dilatation of about 2 per cent. The average dilatation in the effective trials was 34.4 per cent. Two of the dilatations were tremendous—70 and 80 per cent of the original diameter, respectively—while four others lay between 30 and 50 per cent. The remaining six ranged from 5 to 30 per cent. The maximum change in diameter in the six smaller dilatations was reached quite uniformly in one-half minute after the injection was begun. The maximum in the six larger dilatations was reached in a much more variable length of time, ranging from one and three-tenths to thirteen minutes, with an average of seven minutes. There was always rapid dilatation at first in the last group; thus, in one trial the artery dilated 36 per cent in one and one-fourth minute, then hesitated and even constricted slightly for two minutes and finally dilated gradually and steadily in the next seven minutes 70 per cent of its original diameter. After remaining one and one-half minute at the peak of dilatation, the artery decreased in caliber, returning almost, but not quite, to normal in the next twenty-six and one-half minutes. The 80 per cent dilatation was reached in four and one-half minutes (66 per cent dilatation in fifteen seconds—a phenomenal change). The artery remained fully dilated for one hour and fifteen minutes, when the blood pressure fell rapidly and circulation in the artery became so slow that the individual corpuscles could be distinguished. With these two exceptions, maximal dilatation was maintained briefly, never over half a minute, and the normal caliber was regained in from one and one-fourth to twenty-eight minutes.

Cisternal Pressure: In the six trials in which cisternal pressure was recorded it invariably rose. The maximum increase in pressure ranged from 14 to 175 mm. of water and usually occurred within the first thirty seconds. In all but one trial the peak of increased pressure lasted half a minute. In the trial in which the pressure rose to 175 mm. of water the peak lasted twelve minutes. (This was the trial in which the artery dilated 80 per cent of its diameter and remained fully dilated for over an hour.)

Arterial Pressure: As in the intravenous series, the arterial pressure exhibited four types of behavior (table 4). In the first group were four trials in which the arterial pressure was unchanged. In the other three groups there were seven trials in which the pressure either rose or fell or first fell and then rose. None of these changes was as great in magnitude as those in the intravenous series. In one trial arterial pressure was not recorded. The maximum change in blood pressure in groups II and III and the first phase of change in group IV were reached in from three-tenths to seven-tenths minute. In general, the peak of arterial pressure was maintained only for a few seconds, and the pressure returned to normal in from one to three minutes.

Correlation of Arterial Caliber, Dose, Rate of Injection and Cisternal and Arterial Pressures: Inspection of table 4 gives evidence that dila-

tation was independent of changes in arterial pressure. Thus, dilatation of 70 per cent occurred with no associated change in arterial pressure. In group III the dilatations associated with a fall in arterial pressure seem smaller, but in the two instances in which dilatation was slight the dose was much smaller than in the other trials. On the two occasions when tremendous dilatation was observed, alcohol was administered in a 25 per cent solution, and it is likely that, without the opportunity for admixture with the blood which follows intravenous injection, this more concentrated solution had a toxic effect out of proportion to the actual dose, which was the same whether the alcohol was in a 10 or a 25 per cent solution. While changes in arterial caliber

TABLE 4.—*Response of Arterial Pressure, Cisternal Pressure and Diameter of the Pial Artery to Intracarotid Injection of Alcohol*

Group	Response of Arterial Pressure	Number of Trials	Dose of Absolute Alcohol, Cc. per Kg.	Solution of Alcohol Given, Percentage	Length of Period of Injection, Min.	Change in Cisternal Pressure, Mm. of Water	Change in Arterial Pressure, Mm. of Mercury	Arterial Dilatation, Percentage
I	No change.....	4	0.2	10	0.17		0	29.0
			0.2	25	0.25		0	70.0
			0.2	10	0.66	+14	0	14.3
			0.2	25	0.13		0	12.25
II	Rise.....	2	0.2	10	0.50	+46	+12	47.0
			0.2	10	0.42	+46	+20	47.9
III	Fall.....	3	0.1	10	0.25		—16	7.9
			0.05	10	0.16		— 6	5.9
			0.2	10	0.50	+76	— 6	19.0
IV	First fall, then rise	2	0.2	25	0.3		{—14 {+24	46.0
			0.15	25	0.16	+175	{—22 {+10	80.0

were much greater than in the series of intravenous injections, the changes in arterial pressure were less pronounced, which is added proof that the dilatation is a direct effect of the alcohol. The rise in the cisternal pressure was in some degree commensurate with the increase in arterial caliber. The blanching of the artery as it became empty of red corpuscles was a phenomenon which was not observed in the series of intravenous injections. It was noted after all intracarotid injections of a 25 per cent solution of alcohol and all but one injection of equivalent doses of a 10 per cent solution. After injections of the three smaller doses blanching did not occur, although the volume of fluid injected was equivalent to some doses of the 25 per cent solution.

Controls: As in the preceding series, observations over long periods showed no significant spontaneous fluctuations in the caliber of the pial arteries selected. Ringer's solution equal in volume to the volume of alcohol given was injected at the same speed, and no change in arterial caliber occurred. The maximum

change in cisternal pressure after injection of Ringer's solution was a rise of 10 mm. of water. The arterial pressure was usually unaffected. No blanching of the artery was noted after injection of the solution used as a control.

3. *Intracarotid Injection of Alcohol in an Unanesthetized Cat.*—One unanesthetized cat was prepared with a cranial window by a method I have previously described.[19] One-tenth cubic centimeter of absolute alcohol per kilogram of body weight in a 10 per cent solution was injected into the left carotid artery in thirteen seconds. This dose was only from one-half to two-thirds as large as that in intra-

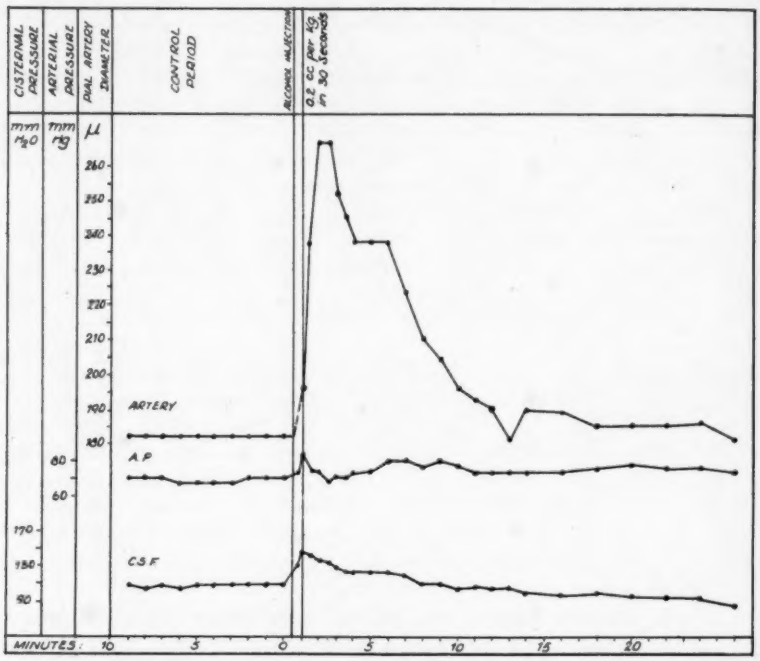


Fig. 6.—Dilatation of the pial artery in response to injection of 10 per cent alcohol into the left carotid artery (cat 23, trial 1). The artery dilated 47 per cent after a brief period of blanching, indicated by the dotted line.

carotid injections given to anesthetized cats. No determination of the arterial or the cisternal pressure was made on the unanesthetized animal, but the pial artery was accurately observed, as usual. Within twenty seconds after the beginning of the injection the artery had dilated 19.1 per cent; one minute later it had returned to the normal caliber. There was no blanching of the artery, nor was any constriction noted.

19. Thomas, C. B.: Constriction of Pial Vessels in the Unanesthetized Cat Produced by Stimulation of the Cervical Sympathetic Chain, Am. J. Physiol. **114**:278, 1936.

4. *Administration of Alcohol by Stomach Tube in Anesthetized Cats.*—Alcohol in a 25 and a 30 per cent solution was administered by stomach tube to five cats under dial anesthesia.

Dosage: Larger doses were given than in the preceding experiments; the total dose ranged from the equivalent of 3.25 to that of 19 cc. of absolute alcohol per kilogram of body weight. Three cats received only a single dose; the largest of these was 9 cc. per kilogram. The cat receiving this dose was moribund an hour and three quarters later. The other two cats received a total of 6.25 and 11 cc. per kilogram, respectively, the first amount being given in three doses, at intervals of an hour and the second in four doses, at intervals of from ten to twenty minutes.

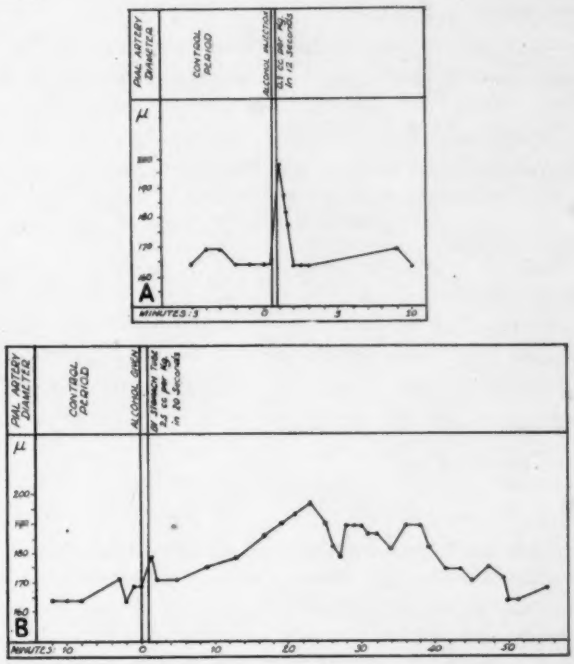


Fig. 7.—Dilatation of the pial artery in an unanesthetized animal (cat 28). *A* shows the response to injection of 10 per cent alcohol into the left carotid artery, and *B*, that to the administration of alcohol by stomach tube.

Caliber of the Pial Artery; Cisternal and Arterial Pressures: No dilatation of the pial artery was noted at any time, except transiently after vomiting and during terminal asphyxia. The diameter of the vessel, and the arterial and cisternal pressures frequently remained unchanged for an hour or more after the alcohol was given. Toward the end of each experiment the arterial and cisternal pressures fell. When constriction occurred, it was usually preceded and accompanied by falling arterial pressure, sometimes to shock levels.

5. *Administration of Alcohol by Stomach Tube to Unanesthetized Cats.*—The equivalent of 2.5 cc. of absolute alcohol per kilogram of body weight in a 25 per cent solution was administered by stomach tube

to an unanesthetized cat with a cranial window. Slow, steady dilatation began at once, reaching a peak of 16.6 per cent in twenty-three minutes. This was maintained for less than two minutes, when the artery began to constrict and reached its original base line fifty minutes after the alcohol was administered. The equivalent of 3 cc. of absolute alcohol per kilogram was administered in a 25 per cent solution by stomach tube to a cat without a cranial window. At the end of three minutes the cat was slightly subdued, and at the end of eight minutes, more subdued and slightly unsteady. At the end of twenty-five minutes the animal showed extreme incoordination and at the end of twenty-eight minutes fell asleep.

6. *Experiments on Anesthetized and Unanesthetized Rabbits.*—Three experiments were carried out on rabbits weighing from 3.5 to 4.5 Kg.

TABLE 5.—*Response of the Caliber of the Pial Artery and Arterial and Cisternal Pressures to Intravenous Injection of Alcohol in Unanesthetized Rabbits*

Trial Number	Dose of Absolute Alcohol, Cc. per Kg.	Rate of Injection, Cc. per Min.	Change in Cisternal Pressure, Mm. of Water	Change in Arterial Pressure, Mm. of Mercury	Change in Caliber of Pial Artery, Percentage	
					Constriction	Dilatation
I-1	0.9	0.24	+6	{+10 {−24	0	37.0
I-2	0.3	0.09	−6	+ 4	0	18.6
II-1	0.5	0.25	...	+14	5	0
II-2	1.0	0.66	...	+30	5	15.0
II-3	1.25	0.57	...	−14	0	4.3
II-4	1.25	0.21	...	+20	0	21.7

The first rabbit was fully anesthetized with pentobarbital sodium. Four doses of 0.2 cc. of absolute alcohol per kilogram of body weight in a 10 per cent solution were injected into the left carotid artery, with the cranial window in the left parietal region. In each case the artery blanched and then dilated 62 per cent on the average in sixty-five seconds, returning to the normal caliber in from three to nine minutes. The arterial pressure rose momentarily in three trials and returned to normal by the time the peak of dilatation was reached. In the fourth trial the pressure was elevated 22 mm. at the peak of dilatation.

In the remaining two rabbits the cranial window was inserted in the usual way, with the animal under ether anesthesia; the animals were then allowed to recover from the anesthetic. Six intravenous injections of 25 per cent alcohol were made, ranging in dose from 0.3 to 1.25 cc. of absolute alcohol per kilogram of body weight (table 5). The injections were completed in from one to six minutes. Dilatation followed injection in five of the six trials. The dilatations ranged from 4.3 to 37 per cent, with an average of 19.3 per cent. In two instances early constriction of 5 per cent occurred, in one followed by dilatation and in the other not. The arterial pressure rose in four instances, fell once and first rose and then fell once (a reaction opposite to that noted in group IV in the series of intravenous experiments on cats). The cisternal pressure, recorded only in the first

rabbit, was little affected. The two constrictions occurred thirty and fifty seconds after injection was started. The peak of dilatation was reached in a minute and a quarter in both trials in the first rabbit and in four and a quarter minutes, one minute and one minute in the second rabbit.

After the injections described had been performed, 5 and 10 per cent dilutions of alcohol in Ringer's solution were introduced through the wash-out vents beneath the windows in rabbits II and III. Both maneuvers were followed promptly by a dilatation of 65 per cent in the vessel under observation. There was no change in arterial pressure. Introduction of Ringer's solution in a similar manner did not produce any change in arterial caliber.

COMMENT

The experiments described in this paper demonstrate that alcohol consistently causes dilatation of the arteries of the pia mater. This dilatation is produced by intravenous and intracarotid injections of alcohol and by its local application in both anesthetized and unanesthetized cats and rabbits. The average degree of dilatation in the two species is nearly identical—19.5 per cent in cats under anesthesia and 19.3 per cent in unanesthetized rabbits. When the cats are anesthetized with dial, dilatation of pial vessels does not occur after the administration of alcohol by stomach tube. Since gastric absorption is retarded by anesthesia, the concentration of alcohol in the blood at any given time may be insufficient to produce dilatation. This could be shown by comparing the concentrations of alcohol in the blood of anesthetized cats with those of unanesthetized cats after the introduction of alcohol into the stomach.

The dilatation does not depend on a rise in general arterial pressure, since it occurs in experiments in which the arterial pressure falls and in those in which it remains unchanged. In the instances in which the arterial pressure rises, there is, moreover, no correlation between this rise and the degree of dilatation of the pial arteries.

The maximum dilatation is brief, usually less than a minute, and the whole period of dilatation lasts less than twenty-five minutes after injection into a blood vessel. The duration of the change in caliber is roughly proportional to the size of the effective dose and the magnitude of the dilatation. In the few instances in which the vessel remained fully dilated for a prolonged period, the subsequent circulatory collapse and death of the animal demonstrated the high toxicity of the dose. All the other animals survived.

The extent of the dilatation after injection of alcohol into the carotid artery is so much greater than that after injection into the femoral vein that one must conclude that the dilatation is brought about by a local mechanism. It may act directly on the wall of the pial artery or reflexly through the vasomotor center or the carotid sinus or in all, or in any combination of, these ways. Since the "great"

dilatations (from 27 to 47 per cent) formed an isolated group, separated by a wide gap from the groups of small and medium extent, the largest of which was 18 per cent (table 1), it is likely that in these instances the dose comprised a stimulus sufficient to bring into play an additional mechanism associated with a fall in blood pressure.[19a]

The change in color of the blood in the pial veins from blue to red during "great" dilatation of the pial arteries associated with a fall in general arterial pressure indicates speeding up of the blood flow through the capillary bed. In the absence of a rise in general arterial pressure, this must depend on dilatation of the arterioles, with consequent lowering of peripheral resistance. This increased rapidity of blood flow could be observed directly in the veins, which maintained a constant caliber throughout. Under the same conditions, the blood flow deep in the parietal lobe is shown to be increased by the thermo-electric recorder, and at the same time the cerebrospinal fluid pressure rises to a peak.

All these observations give substantial evidence that alcohol produces dilatation not only of the visible pial arteries, which form a small portion of the cerebral vascular bed, but of the deep cerebral arteries and arterioles. The sharp rise in cerebrospinal fluid pressure indicates that the volume of the blood within the cranial cavity is increased. In spite of the fact that there is no general reddening of the surface of the brain beneath the microscope to indicate widespread dilatation of capillaries, it is likely that the capillary bed is increased to accommodate the additional volume of blood.

The response of cerebrospinal fluid pressure to intravenous injections of alcohol[20] has been studied in man by Fleming and Stotz.[21] They noted that cerebrospinal fluid pressure rises sharply in a simple curve and reaches its maximum approximately when the concentration of alcohol in the blood is at its highest; this occurred near the end of the seven minute period of injection. Although studies on blood pressure were lacking, the similarity of these curves for cerebrospinal fluid pressure in man to those obtained in cats and rabbits after comparable

---

19a. Since this paper was written, new observations by H. S. Forbes, G. I. Nason and R. C. Wortman (Cerebral Circulation: XLIV. Vasodilatation in the Pia Following Stimulation of the Vagus, Aortic and Carotid Sinus Nerves, ARCH. NEUROL. & PSYCHIAT. **37**:334 [Feb.] 1937) and M. Fog (Cerebral Circulation: The Reaction of the Pial Arteries to Fall in Blood Pressure, ibid. **37**:351 [Feb.] 1937) have shown that a fall in blood pressure below a critical level causes dilatation.

20. A dose of 0.6 cc. of absolute alcohol per kilogram of body weight, injected in seven minutes.

21. Fleming, R., and Stotz, E.: Experimental Studies in Alcoholism: Alcohol Content of Blood and Cerebrospinal Fluid Following Oral Administration in Chronic Alcoholism and Psychoses, Arch. Neurol. & Psychiat. **33**:492 (March) 1935; personal communication to the author.

intravenous injections of alcohol, as described here, implies similar cerebral vasodilatation in man.

The changes in cerebral circulation indicate that the vessels of the brain respond to alcohol in a characteristic manner, resembling the dilatation of the cutaneous vessels and differing from the constriction of splanchnic vessels caused by the same drug.[22] With alcohol as with histamine, acetylcholine, amyl nitrite and caffeine, the chemical content of the blood is of greater importance than the hydrostatic or systemic blood pressure in the regulation of cerebral circulation.

CONCLUSIONS

1. Alcohol causes dilatation of the pial arteries of cats and rabbits, preceded sometimes by slight constriction.

2. The vasodilatation is independent of changes in the systemic arterial pressure.

3. After the administration of alcohol the systemic arterial pressure may fall or rise or remain unchanged.

4. Alcohol invariably produces a rise in cerebrospinal fluid pressure.

5. Alcohol increases the flow of blood through the brain.

6. During arterial dilatation the flow of blood through the pial veins becomes visibly more rapid, and the color of the vein changes from blue to red.

7. The findings suggest that dilatation occurs in other cerebral arteries and arterioles, as well as in the pial arteries.

Dr. Stanley Cobb and Dr. Henry S. Forbes gave advice in the carrying out of these experiments. Miss Margaret Gray rendered valuable technical assistance.

22. Cook, E. N., and Brown, G. E.: The Vasodilating Effects of Ethyl Alcohol on Peripheral Arteries, Proc. Staff Meet., Mayo Clin. **7**:449, 1932.

EFFECT OF INJECTIONS OF COLLOIDAL THORIUM DIOXIDE ON THE VENTRICLES AND SUBARACHNOID SPACES

WALTER FREEMAN, M.D.
WASHINGTON, D. C.

In the course of studies [1] on the use of colloidal thorium dioxide as an agent for ventriculography a number of surgical and pathologic specimens have been obtained, from which some conclusions may be drawn concerning the effects produced by the injection of this foreign substance. As far as I am aware, there have been no similar studies of the results in man, and the studies on dogs reported by Alexander, Jung and Lyman [2] were made after the intraventricular injection of an unstabilized and unbuffered colloidal suspension of thorium dioxide.

In view of the remarkable ventriculograms obtained after the injection of colloidal thorium dioxide, information is desirable to indicate whether the method is a safe one for more extensive use.

The material on which I am reporting consisted of two specimens obtained for biopsy and material from eight autopsies, the time of securing of which ranged from one hour to two months after the injection of colloidal thorium dioxide into the ventricles and subarachnoid spaces.

An understanding of the resulting changes is facilitated by following the alterations that take place in the medium after its injection. The preparation of thorium dioxide is a buffered colloidal solution, stabilized by a protective colloid consisting of a solution of dextrin. In the course of one or two days after injection into a closed space the protective colloid is dispersed, and the thorium dioxide flocculates, clinging to the walls and eventually forming sheets and plaques, which remain in place for an indefinite period. These plaques have been followed roentgenographically for three months and more and seem to disappear gradually. This observation applies, however, only to the material in closed cavities. When the ventricular system is unobstructed the colloidal suspension is maintained until the foreign material is eliminated from the cranial cavity

---

From the George Washington University School of Medicine.

Read at a meeting of the American Association of Neuropathologists, Atlantic City, N. J., June 1, 1936.

1. Freeman, W.; Schoenfeld, H. H., and Moore, C.: Ventriculography with Colloidal Thorium Dioxide Solution, J. A. M. A. **106**:96 (Jan. 11) 1936.

2. Alexander, L.; Jung, T. S., and Lyman, R. S.: Colloidal Thorium Dioxide: Its Use in Intracranial Diagnosis and Its Fate on Direct Injection into the Brain and the Ventricles, Arch. Neurol. & Psychiat. **32**:1143 (Dec.) 1934.

(at least in amounts demonstrable by roentgen rays) along the normal pathways of absorption of the cerebrospinal fluid. At necropsy in one case particles of thorium dioxide were observed in the arachnoid villi and the longitudinal sinus itself, mixed with a terminal clot.

ALTERATIONS IN THE BRAIN AFTER INJECTION OF COLLOIDAL THORIUM DIOXIDE

Choroid Plexus.—Within an hour after injection of thorium dioxide into the ventricles, there is beginning exudative inflammation affecting

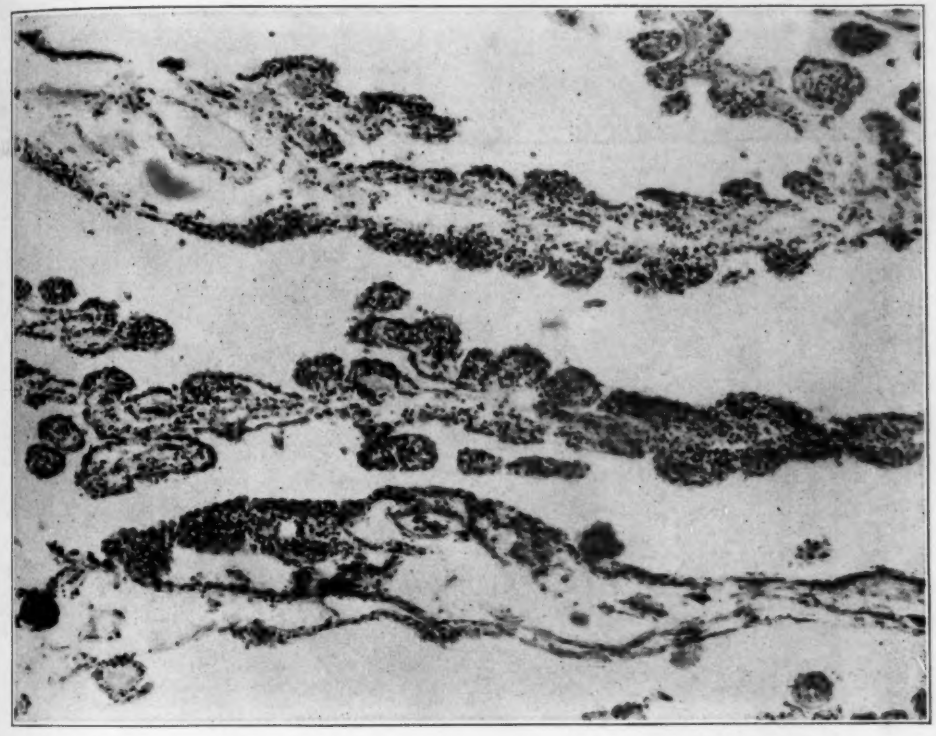


Fig. 1.—Choroid plexus twenty-four hours after the intraventricular injection of colloidal thorium dioxide. This reaction subsides in four days.

the choroid plexus, which consists in swelling of the choroidal epithelium and the presence of an occasional leukocyte on the surface. A few granules of thorium dioxide are visible adhering to the choroidal surface.

Within twenty-four hours this inflammation is well marked (fig. 1), consisting of edema and fairly marked leukocytic infiltration, engorgement of the veins and some destruction of the epithelium. The epithelial cells elsewhere are swollen and granular, and a few macro-

phages make their appearance, the cytoplasm of the latter and even of some of the leukocytes containing granules of thorium dioxide.

In the course of another three days, however, the choroid plexus is reestablished to a practically normal degree, and inflammatory signs are no longer present. A few macrophages are still adherent to the surface.

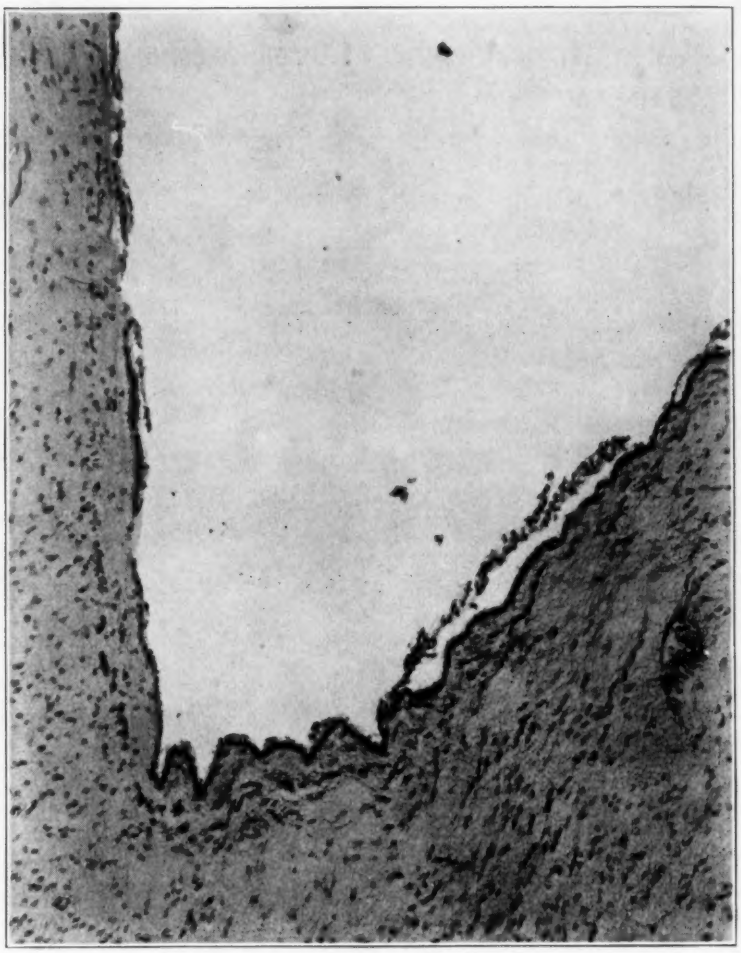


Fig. 2.—Ependymal degeneration and desquamation twenty-four hours after injection of 5 cc. of colloidal thorium dioxide into the occluded ventricle.

Ependyma.—No reaction is observed in the ependyma earlier than twenty-four hours, and even then grossly nothing is seen except minute glistening nodules that consist of particles of the material deposited on the ependymal surface. Microscopically there are swelling of the

ependyma and beginning exfoliation. Over the surface, partly adherent, may be observed masses of leukocytes and macrophages, both containing particles of thorium dioxide. There is little or no reaction in the subependymal tissue. Figure 2 was taken in a case in which the interventricular foramen was blocked and the material was introduced only into the ventricle opposite the tumor.

Four days after the injection in a case of obstructive hydrocephalus, extensive alterations in the ependyma were observed. In this case the

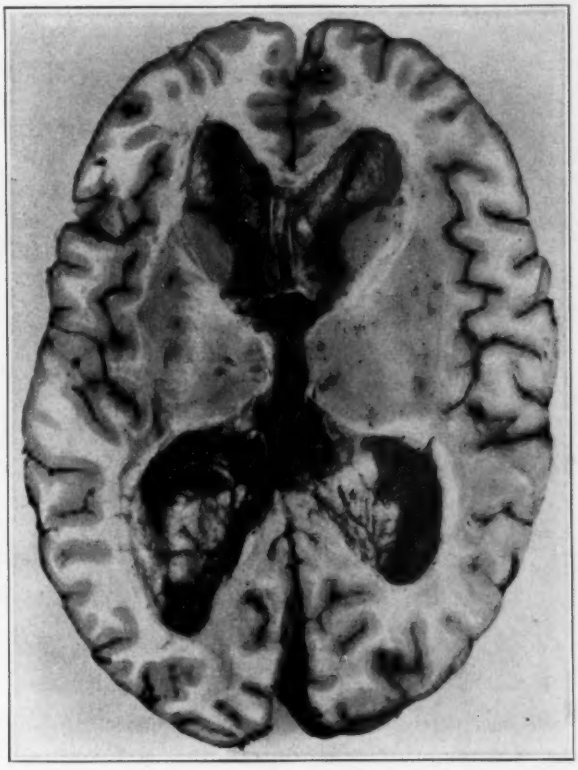


Fig. 3.—Horizontal section of the brain in a case of obstructive hydrocephalus due to preexisting meningitis, four days after the injection of 10 cc. of colloidal thorium dioxide. Petechial hemorrhages are evident.

ventricles were filled with pus of rather thin, granular character, in which many leukocytes were observed on smear, mingled with macrophages. The ependymal veins showed considerable engorgement, and numerous minute focal hemorrhages were seen in the ependymal lining (fig. 3). Microscopically there was widespread exfoliation of the ependymal lining, accompanied by perivascular exudation of leukocytes

about the regional veins (fig. 4). Over the denuded surface there were masses of cellular exudate, consisting of leukocytes, macrophages and a few lymphocytes, mingled with both free and intracellular particles of thorium dioxide. The reaction in the subependymal tissue was difficult to estimate on account of the presence of preexisting ependymitis, which had accompanied the meningeal infection years previously. At all events, there were only slight alterations in the adjacent astrocytes.

Two months after the injection in a case of ventricular obstruction caused by a tumor of the pons, associated with marked dilatation of the

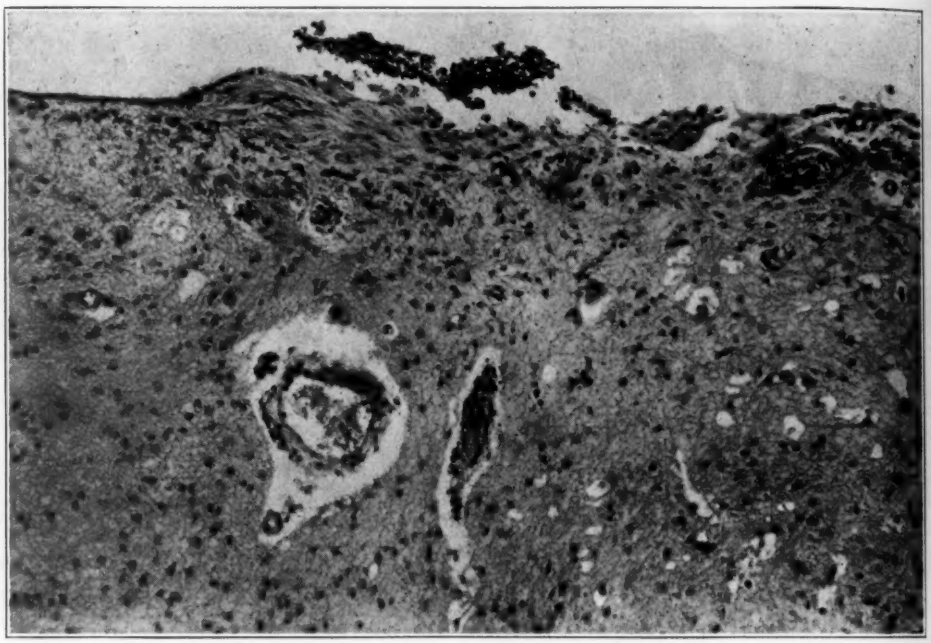


Fig. 4.—Ependymal desquamation and regional inflammatory changes in the same brain as that shown in figure 3. An aggregate of thorium particles mixed with leukocytes and histiocytes is adherent to the surface. The subependymal gliosis is old.

third ventricle, the ependyma was largely absent; in its place, on the bare fibrous glial lining, there was a thin sheet of histiocytes containing particles of thorium, with occasional aggregates of larger size. These were usually disklike or oval in cross-section and consisted of histiocytes, filled with the foreign material and enmeshed in a reticulum of glia fibers with few remaining ependymal cells, and little reaction in the deeper layers (fig. 5). Nevertheless, a few histiocytes were observed

at some depth below the ventricular surface. No perivascular infiltrations were observed.

Meninges.—The first demonstrable reaction occurs in the meninges about twenty-four hours after injection, although there is clinical evidence of irritation somewhat earlier, manifested by headache and some stiffness of the neck. This reaction consists of leukocytic exudation, some of the leukocytes containing the injected particles. The superficial distribution of the exudate indicates that the cells are derived from the ventricles rather than poured out locally. Even at this time, however, macrophages are present and have phagocytosed many of the particles. At the end of two days the leukocytes disappear, and the macrophages

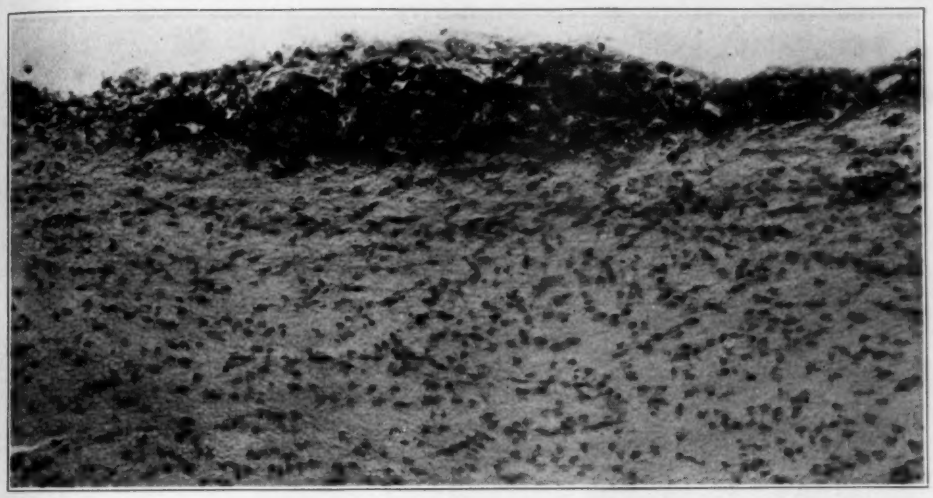


Fig. 5.—Lining of the third ventricle in a case of obstruction two months after injection of colloidal thorium dioxide. The histiocytes containing the thorium particles are buried in a tangle of glia fibers. The ependyma is desquamated.

increase in number. After six days in a case in which the injection had been made by mistake into the interhemispheric subarachnoid space, the meningeal reaction was pronounced both grossly and histologically, but the cells consisted almost entirely of histiocytes. There was no fibrin or plastic inflammation, and much of the thorium was still free in the meningeal spaces, usually clumped together in the form of minute globules.

In a case in which the patient died after two months and necropsy was performed, the meninges were perceptibly thickened about the base but relatively little elsewhere, and there was no indication of matting, with blocking of the cerebrospinal fluid pathways. The details of this reaction are seen in figure 6. A few lymphocytes were present, but

most of the cells were macrophages. A large proportion of the thorium still remained free in the meningeal spaces, indicating its great inertness.

Colloidal thorium dioxide was injected into the cistern in certain cases in an effort to fix it in the meninges in order to obtain a picture of the spinal cord of a person with a nonobstructive lesion. Thus far, however, my colleagues and I have available for study only a specimen in which there were two small tumors on the roots of the cauda equina,

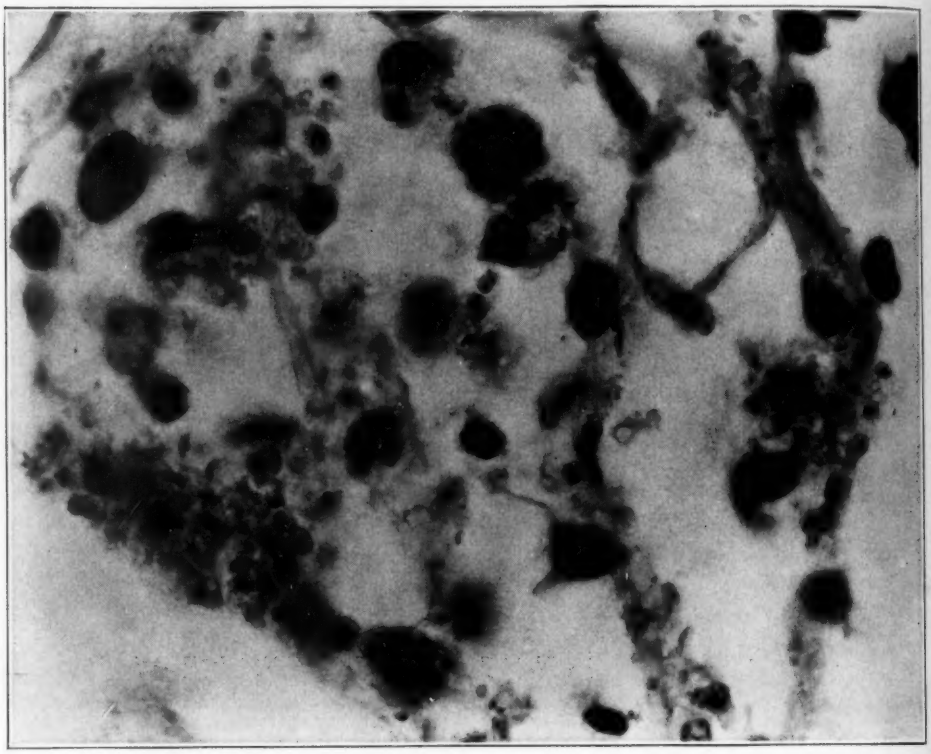


Fig. 6.—Meninges over the cerebellum two months after the injection of thorium dioxide in the same case in which the reaction is shown in figure 5. A few lymphocytes and fibroblasts are present, but most of the cells are histiocytes. Much of the thorium dioxide lies inert in the pial meshes.

the patient dying of urinary sepsis about two weeks after lumbar injection of the material. There was no exudative inflammation about the spinal cord, although particles of thorium were observed in the cerebral meninges. Small quantities of the thorium had been taken up by the macrophages distributed here and there in the subarachnoid spaces of the spinal cord, and especially in the neighborhood of the tumor masses.

COMMENT

Pathologic changes following injection of colloidal thorium dioxide into the ventricles begin with leukocytic exudation from the choroid plexus within an hour. In twenty-four hours this is well marked, and there are beginning desquamation of the ependyma and meningeal exudation. The inflammation of the choroid plexus subsides within four days. In cases of obstruction the ependyma shows continued changes of considerable severity, leading finally to its destruction and the flocculation of the thorium particles on the denuded surface, where they are taken up by the macrophages and effectively entombed in a feltwork of glia fibers.

The meningeal reactions are leukocytic in the earlier stages but subside quickly, the place of the leukocytes being taken by macrophages, mixed with a few lymphocytes. Lange [3] reported the presence of eosinophils in the spinal fluid two or three days after subarachnoid injection. The great inertness of the thorium is indicated by the presence of unphagocytosed particles two months after injection.

Two questions remain for future decision. Alexander, Jung and Lyman showed photographs suggesting that the macrophages are ependymogenous. I observed no comparable pictures and am inclined to attribute the origin of the macrophages to the blood stream via the choroid plexus. The second question concerns the ultimate fate of the thorium and its effect on the tissues, especially from the standpoint of possible radio-activity. In the small quantities injected and with the rapid disappearance of most of the material, it is unlikely that serious after-effects would ensue, particularly since normal cerebral tissue is notoriously unsusceptible to radiant energy. The inertness of the thorium also precludes the possibility of further progressive local inflammatory reaction, with the formation of a granulomatous lesion.

SUMMARY

Stabilized colloidal thorium dioxide exerts a transitory inflammatory reaction in the choroid plexus, ependyma and meninges. In cases of ventricular obstruction profound inflammatory changes may ensue, with suppurative ependymitis, desquamation of the ependyma and formation of plaques and masses of thorium in phagocytes on the denuded surface of the ventricles.

3. Lange, O.: Considérations sur l'éosinophilie du liquide céphalorachidien, Rev. neurol. **64**:512 (Oct.) 1935.

PSYCHOSES ASSOCIATED WITH PERNICIOUS ANEMIA

M. HERMAN, M.D.

HARRY MOST, M.D.
AND
NORMAN JOLLIFFE, M.D.
NEW YORK

The occurrence of mental changes in patients having pernicious anemia was noted by Addison[1] in his classic description of the disease in 1855. Psychiatric studies of patients with this disease have since appeared only at infrequent intervals, though there are many contributions from an etiologic, neurologic and hematologic standpoint.[2] This poverty of psychiatric reports exists in spite of the high incidence of mental changes in this disease, as evidenced by the recent work of Goldhamer and his associates,[3] who reported that 64 per cent of their patients showed cerebral symptoms. Other observers, however, reported the incidence of mental changes to be from 25 to 40 per cent; for instance, Ahrens [4] reported 25 per cent, Woltman [5] 39 per cent, Hulett [6] 35 per cent and Weisenburg [7] 40 per cent. Mental symptoms in patients with pernicious anemia that are sufficiently severe to be classi-

From the Departments of Psychiatry and Medicine, New York University College of Medicine, and the Psychiatric Division and the Psychiatric Medical Service of the Third (New York University) Medical Division of the Bellevue Hospital.

1. Addison, T.: Anemia: Disease of the Suprarenal Capsules, London M. Gaz. **43**:517, 1855.

2. Sturgis, C. C.; Isaacs, R.; Goldhamer, S. M.; Bethell, F., and Farrar, G. E.: Blood: A Review of the Recent Literature, Arch. Int. Med. **55**:1001 (June) 1935.

3. Goldhamer, S. M.; Bethell, F. H.; Isaacs, Raphael, and Sturgis, Cyrus C.: The Occurrence and Treatment of Neurologic Changes in Pernicious Anemia, J. A. M. A. **103**:1663 (Dec. 1) 1934.

4. Ahrens, R. S.: Neurologic Aspects of Primary Anemia, Arch. Neurol. & Psychiat. **28**:92 (July) 1932.

5. Woltman, H. W.: Mental Changes Associated with Pernicious Anemia, Am. J. Psychiat. **3**:435 (Jan.) 1934.

6. Hulett, A. G.: The Psychological and Medicolegal Aspects of Pernicious Anemia, M. J. & Rec. **127**:1 (Jan. 4) 1928.

7. Weisenburg, T. H.: Neurological Symptoms Occurring in Pernicious Anemia, Especially Antedating the Appearance of the Blood Picture, M. Rec. **99**:942 (May 28) 1921.

fied as a psychosis are less common. Cabot,[8] in a series of 600 cases of pernicious anemia, found that 16 per cent of the patients were psychotic, while Woltman,[5] in a series of 1,498 cases, and Smithburn and Zerfas[9] found the incidence to be 4 and 6 per cent, respectively. Though psychosis is rather common in patients with pernicious anemia, pernicious anemia in psychotic patients is comparatively rare. Bowman,[10] in analyzing the cases at the Boston Psychopathic Hospital during a period of fourteen years, found the incidence to be 0.08 per cent.

The literature reveals a varied mental picture in psychotic patients with pernicious anemia, a fact noted by Addison. Barrett[11] studied 11 subjects, of whom 2 had epilepsy, 2 a psychosis resembling schizophrenia and 1 a condition resembling a manic-depressive psychosis and the remaining 6 presented an asthenic state with a paranoid type of psychosis. Barrett's subjects presented in common irritability and suspiciousness, which formed the groundwork for delusions of persecution. Hulett[6] also reported the most frequent type of psychosis to be a paranoid state with delusions of persecution and of grandeur. Camp[12] described the case of a patient having delusions of grandeur resembling those associated with dementia paralytica and mentioned 2 similar cases. Williams[13] reported 2 cases of a condition that resembled a toxic psychosis, and some[14] have reported cases in which there was a Korsakoff syndrome. From a study of 7 cases, Pickett[15] described the composite mental picture as shallow confusion with disorientation, illusions of identity and, less commonly, hallucinations and persecutory delusions. Ahrens[4] expressed the belief that the most common mental picture is one of slow cerebration with impairment of memory. Goldhamer and his co-workers[3] held mild depression, irritability and disturbances in

---

8. Cabot, quoted by Rogers, A. W.: Disturbances of the Central Nervous System Accompanying Pernicious Anemia: Report of Two Cases, J. Nerv. & Ment. Dis. **43**:693, 1915.

9. Smithburn, R. C., and Zerfas, L. G.: The Neural Symptoms and Signs in Pernicious Anemia: Effects of Liver Extract, Arch. Neurol. & Psychiat. **25**: 1100 (May) 1931.

10. Bowman, K. M.: Psychoses with Pernicious Anemia, Am. J. Psychiat. **92**:371 (Sept.) 1935.

11. Barrett, A. M.: Mental Disorders and Cerebral Lesions Associated with Pernicious Anemia, Am. J. Insanity **69**:1063, 1913.

12. Camp, C. C.: Pernicious Anemia Causing Spinal Cord Changes and a Mental State Resembling Paresis, M. Rec. **81**:156 (Jan. 27) 1912.

13. Williams, G. H.: The Psychosis Occurring During the Course of Pernicious Anemia, J. A. M. A. **63**:936 (Sept. 12) 1914.

14. Bonhoffer, K.: Ueber psychische Störungen bei anämischen Prozessen, Berl. klin. Wchnschr. **48**:2357, 1911. Parfitt, D. N.: Psychoses Associated with Pernicious Anemia, J. Neurol. & Psychopath. **15**:12 (July) 1934.

15. Pickett, W. R.: Mental Symptoms Associated with Pernicious Anemia, Am. J. M. Sc. **127**:1032 (June) 1904.

memory to be the most frequent mental symptoms. Hunt [16] described the early mental changes in patients with pernicious anemia as apathy, indolence, indifference and abnormalities of conduct. He expressed the opinion that the most usual psychosis is of a paranoid type, but he found no characteristic trend in the mental content. Atkin [17] noted that mental symptoms may appear before the anemia is recognized or may be so prominent that the underlying state of the blood is overlooked. Some authors [18] have described a prepernicious anemia mental change.

The changes in personality of patients with pernicious anemia while under treatment are well known. It is a common clinical observation [10] that a patient in a relapse of the disease frequently shows marked irritability and peevishness but that when he is treated with a potent liver preparation the time of the reticulocyte response can often be predicted by the disappearance of irritability and peevishness. Richardson [19] noted that after adequate treatment stubbornness, surliness, obstinacy and disagreeableness often change to smiling amiability.

In the five year period from 1931 to 1935, inclusive, 40 patients suffering from pernicious anemia were studied in the medical service of the psychiatric division of the Bellevue Hospital. In reporting this group of cases it is our purpose to indicate the incidence of mental disease, classify the psychotic manifestations, analyze the factors underlying the development of the psychosis and indicate a therapeutic approach to the mental symptoms.

During this five year period, 255 patients were admitted to the Bellevue Hospital and discharged with the diagnosis of pernicious anemia. Of this group, 40 subjects were treated in the medical service of the psychiatric division. This number indicates an incidence of 15.7 per cent of psychosis in this group of subjects. During the same five year period about 50,000 nonalcoholic patients were admitted for observation to the psychiatric division of the Bellevue Hospital. These figures indicate an incidence of pernicious anemia of 0.08 per cent in the group of patients admitted for mental observation. The age, sex and death distribution of the patients are tabulated in table. 1. Thirty-three of the 40 subjects were above the age of 50 years, which is in accord with the general experience concerning the age incidence of this

16. Hunt, E. L.: Neurological and Mental Symptoms of Pernicious Anemia, New York State J. Med. **34**:99 (Feb. 1) 1934.

17. Atkin, I.: A Case of Pernicious Anemia Associated with Mental Disease, Lancet **2**:569, 1932.

18. Langdon, F. W.: Nervous and Mental Manifestations of Prepernicious Anemia, J. A. M. A. **45**:1635 (Nov. 25) 1905. Weisenburg.[7]

19. Richardson, W.: Pernicious Anemia: The Results of Treatment with Liver or Its Derivatives in Sixty-Seven Cases, New England J. Med. **200**:540 (March 14) 1929.

disease. The preponderance of females (29 females to 11 males) is noteworthy, since among the 215 patients with pernicious anemia treated in the general hospital the males predominated 6 to 5. The preponderance of females in our psychotic series may be due to a peculiar psychologic significance of this disease for the female.

The type and frequency of the neurologic changes observed in our patients are tabulated in table 2. Neurologic evidence of involvement of the spinal cord occurred in 29, or 72.5 per cent, of our subjects. The high incidence of neurologic involvement indicates in a general way the severity of the disease in this group of patients. However, there

TABLE 1.—*Age, Sex and Death Distribution of 40 Patients Having a Psychosis and Pernicious Anemia*

Age	Male	Female	Deaths
20-29	0	1	0
30-39	0	0	0
40-49	2	4	1
50-59	2	11	2
60-69	5	5	1
70-79	2	8	5
Total	11	29	9

TABLE 2.—*Type of Neurologic Involvement in 40 Patients Having a Psychosis and Pernicious Anemia*

Neurologic Involvement	Number	Percentage
Combined system involvement	17	42.5
Involvement of posterior columns alone	8	20.0
Involvement of lateral columns alone	4	10.0
No signs referable to involvement of cord but other neurologic signs	5	12.5
No neurologic signs	6	15.0
Total showing involvement of cord	29	72.5
Total showing no involvement of cord	11	27.5

is no correlation between the severity of the changes in the spinal cord and the psychosis. The most severe lesions of the cord existed in the presence of relative mental normality, and vice versa. Grinker and Kandel [20] reported the incidence of involvement of the spinal cord as 30 per cent. Goldhamer and his associates [3] found an incidence of neurologic involvement of 90 per cent, while others [2] found an incidence of involvement of the cord of 70 per cent. Smithburn and Zerfas [9] studied 31 subjects showing severe involvement of the spinal cord, and of these only 3 were psychotic. They inferred from this that there is no definite correlation between the severity of the changes in the spinal cord and the development of psychosis.

20. Grinker, R. R., and Kandel, E.: Pernicious Anemia: Results of Treatment of the Neurologic Complications, Arch. Int. Med. **54**:851 (Dec.) 1934.

The red blood cell count on admission was below 1,000,000 per cubic millimeter in 6 of our subjects, below 2,000,000 in 19 and below 3,000,000 in 30. The anemia plays an important part in the production of the psychotic state; however, as we shall point out later, it is only one factor. In our series of 40 cases there were 9 deaths, a mortality rate of 22.5 per cent (table 3). In the general hospital series during the same period the mortality rate was 11.2 per cent. As we shall point out later, certain types of psychosis in a patient with pernicious anemia indicate an unfavorable prognosis. Our figures, however, compare favorably with Bowman's [10] figures obtained at the Boston Psychopathic Hospital, where there were 8 deaths in 22 cases, a mortality rate of 36 per cent.

TABLE 3.—*Clinical Data on 9 Patients Having a Psychosis and Pernicious Anemia Who Died*

Patient	Age	Sex	Red Blood Cells, Millions	Hemoglobin, Gm.	Complications	Mental Diagnosis
L. P.	72	F	0.75	2.8	Arteriosclerosis	Confusional state
M. D.	52	F	1.04	5.0	Thrombosis of left middle cerebral artery	Confusional state
E. S.	72	F	1.01	4.7	Arteriosclerosis	Confusional state
R. B.	48	F	1.70	6.2	None	Confusional state
W. P.	67	M	3.30	11.2	Lobar pneumonia; pyelitis	Confusional state
M. P.	73	F	3.20	9.0	Arteriosclerosis	Confusional state
C. H.	74	F	2.70	10.5	Bronchopneumonia; arteriosclerosis	Organic psychosis
B. C.	70	F	0.60	3.0	Arteriosclerosis	Organic psychosis
J. S.	59	F	3.90	11.4	Fractured femur; ascending infection of urinary tract	Paranoid state

In analyzing the mental symptoms presented in our 40 cases we found, in addition to the independent mental states, four well defined clinical types: an acute confusional state, a paranoid condition, an affective reaction and an organic deterioration type. The psychotic manifestations presented by the patients with each type will be described, with illustrative protocols giving pertinent data.

ACUTE CONFUSIONAL STATE

This was the most frequent type of mental picture, occurring in 14, or 35.0 per cent, of our cases. It was characterized by a fairly rapid change in the state of consciousness which varied from apathy to stupor, but on approaching the patient one could elicit a surprising degree of irritability. Vague hallucinations and illusions, often transitory and changeable, were sometimes present. In some cases there were intense

restlessness and excitement such as are found in a state of delirium. This type of mental reaction was called by Bonhoffer [14] the amentia symptom complex and was in our cases directly related to the degree of anemia. The greater the anemia the more severe was the confusion. Improvement in the mental state paralleled the rise in the level of the red blood cells and hemoglobin. This mental picture in patients with pernicious anemia should be regarded as a serious complication of pernicious anemia in relapse. Of the 9 deaths which occurred in the series of 40 cases (table 3), 6 were in this group of 14 patients. Two of the deaths may be adequately accounted for, by cerebral accident (M. D.) and by pneumonia (W. P.). In L. P. and E. S. there were no major complications. Massive doses of liver were given parenterally, but death resulted in each case on the eighth day of hospitalization, two and three days, respectively, after a transfusion of 500 cc. of whole blood. In R. B., aged 48, the red cell count was 1,700,000 per cubic millimeter and there was no apparent complication. Death occurred on the second day of hospitalization. A blood transfusion was not given. M. P., aged 73, had a red blood cell count of 3,200,000 per cubic millimeter, and no complication was found other than age and arteriosclerosis. The manner of death in these 4 patients was similar. All were admitted in a psychotic state with the mental picture that of severe confusion; all were extremely difficult to feed; all required administration of fluids by hypodermoclysis, and all were so restless as to require side boards attached to the beds. In each sudden collapse occurred, the blood pressure was extremely low or indeterminable and pulmonary edema was present. The deaths of these 4 patients might possibly all have been prevented if we had recognized at that time that this type of mental picture in a patient with pernicious anemia is a serious complication and demands immediate transfusion of blood to sustain life while a hematologic response is induced by parenteral injections of liver extract. In 2 cases transfusions were not given, and in the other 2 they were delayed until the fifth and the sixth day, respectively, after the patient's admission. These 4 deaths occurred during the first three years of this study. We then instituted immediate transfusions of whole blood for every patient with pernicious anemia having a confusional state regardless of the red blood cell level. The transfusions were repeated at daily intervals until definite improvement in the mental picture occurred. In the meantime parenteral injections of liver extract were given, and by the time the reticulocyte response occurred the patient was in a state of relative mental clarity, ate with ravenous appetite and was on the way to a successfully induced remission. Since the adoption and use of this treatment death has not occurred in 4 patients presenting an uncomplicated confusional state.

CASE 1.—A white woman aged 54 was brought directly from her home to the psychiatric division. Her daughter reported that the patient had been noisy and unmanageable for the past few days.

Physical Examination and Course.—The skin had a distinct lemon-yellow color, with an underlying pallor. The gums were badly infected. Neurologic examination showed slight hyperreflexia, with an equivocal Babinski reflex on the left and impaired position and vibratory sense in the lower extremities. The red blood cell count was 1,000,000 per cubic millimeter and the hemoglobin content 4.4 Gm. per hundred cubic centimeters. The color index was 1.2 and the volume index 1.5. Qualitative changes consisted of poikilocytosis, oval macrocytosis, marked polychromatophilia and basophilic stippling. A fractional gastric analysis, after an alcohol test meal, revealed no free acid after the injection of histamine. The patient was given a transfusion of 500 cc. of whole blood; a liver extract containing the material derived from 100 Gm. of whole liver was administered parenterally for three successive days. A reticulocyte response followed, which was succeeded by a gradual increase in the red blood cell and the hemoglobin level. On the patient's discharge, two weeks after her admission, the erythrocytes numbered 3,300,000 per cubic millimeter and the hemoglobin content was 10.7 Gm. per hundred cubic centimeters.

Mental State.—Prior to the hematologic response the only production of the patient was "Oh, doctor, oh, oh!" She was clouded, lethargic, stuporous and deeply confused. When approached she became resentful, irritable and resistive. After the reticulocyte response she became euphoric and overtalkative and at times sang loudly, but she soon returned to her normal state and was discharged without symptoms to the hematologic clinic fourteen days after her admission to the hospital.

Comment.—This subject presented the mental picture typical of the 14 subjects with a confusional state associated with a relapse of the anemia. Soon after the onset of hematologic improvement the mental state cleared rapidly and completely. This patient has shown no abnormal mental symptoms on subsequent observations during the past year in the hematologic clinic.

ORGANIC DETERIORATION TYPE

Five patients showing evidence of progressive organic deterioration represent another clinical group. In patients with a condition of this type there is a gradual disintegration of the mental faculties with impairment of memory, judgment and thinking, and there may be intermittent periods of confusion. When this mental picture occurs in the older age group it resembles the senile or arteriosclerotic type of psychosis. Undoubtedly, in many subjects senility and arteriosclerosis play a large part in producing the clinical pictures. There are, however, subjects in whom no evidence of arteriosclerosis or hypertension is found and the age of the patient is not advanced, yet symptoms referable to an organic deteriorating process in the brain are present. Such a condition may be produced by changes in the brain similar to those noted in the spinal cord, the so-called Lichtheim plaques, the

significance of which, according to Wertham and Wertham,[21] is not understood. Degenerative changes in the brain may also be produced by long-continued anoxemia due to anemia. Whether some unknown toxin [21] or a vitamin-deficient state [22] is another factor in this condition is debatable.

CASE 2.—A white woman aged 62 was transferred from another hospital with a history of symptoms attributable to pernicious anemia for the preceding three months. She was disoriented and had marked impairment of memory, and though specific therapy had been instituted and a satisfactory hematologic response obtained, there had been no improvement in the mental state.

Physical Examination.—The patient was emaciated. An old peripheral facial palsy on the left was noted. The tongue was completely bald. The heart and lungs were normal. The blood pressure was 140 systolic and 90 diastolic. The deep reflexes were equally hyperactive. There were no Babinski reflexes. There was only moderate peripheral arteriosclerosis. The red blood cell count was 4,500,000 and the hemoglobin content 13 Gm. per hundred cubic centimeters. Smears showed slight macrocytosis and some poikilocytosis.

Mental State.—The patient said: "I'm very much better than I was. I have a terrible headache. I don't remember the name of this hospital. Sam works up in that place; I forgot where. I am here about four weeks (on the first day of admission). I was married in 1870 (incorrect). I don't know when I was born but I am 62 years old. I haven't got anything in my head." This patient showed disorientation as to time and place. There was marked gross impairment of memory and intellect. There were no hallucinations or delusional formations. The husband confirmed the history that she had suffered from a gradual severe impairment of memory. The patient was finally committed unimproved to a state hospital.

Comment.—This patient had a typical organic cerebral syndrome occurring in the course of pernicious anemia. The condition was not of the confusional or toxic type, as it was characterized by lack of hallucinations and delusions of the sort found in toxic psychoses. It should be noted that the condition persisted in spite of an approximately normal blood picture. The organic cerebral changes are apparently irreversible. Two of the patients showing this type of mental picture died (table 3), 1 of lobular pneumonia and 1, who entered the hospital in a moribund state, in a severe relapse of the anemia.

PARANOID CONDITION

The paranoid type of psychosis occurred in 7, or 17.5 per cent, of our patients. This mental reaction was characterized as a rule by a systematized delusional picture in a state of mental clarity. The complaints of these subjects were that some member of the family,

21. Wertham, Frederick, and Wertham, Florence: The Brain as an Organ, New York, The Macmillan Company, 1934.

22. Gildea, E. F.; Kattwinkel, E. E., and Castle, W. B.: Experimental Combined System Disease, New England J. Med. **202**:523 (March 13) 1930.

an acquaintance, the police or simply "they" were persecuting the patient by attempts to injure or kill him by the administration of poison. The physical disabilities, the paresthesias, the sore tongue, the diarrhea, all were attributed to this persecution. This reaction develops, we believe, through a combination of factors in which the psychogenic elements plays a prominent rôle. Pernicious anemia at times produces disturbing symptoms, such as paresthesias and somatic sensations, which the patient cannot understand. The patient is frequently considered neurotic by friends and relatives, and too often a physician corroborates this diagnosis. Weakness and symptoms of the advancing neurologic changes develop. Urinary incontinence often occurs, with the result that the patient's attention is directed to the genitalia. Bender [23] has shown in pernicious anemia and in other diseases, such as cretinism, osteogenesis imperfecta, Paget's disease, Little's disease and poliomyelitis, that similar factors are important in the production of mental symptoms. The diseases that distort the postural model of the body [24] produce psychic attitudes and a feeling of inferiority that make delusional states with paranoid projections relatively common. To the female these physical symptoms or postural distortions have a greater psychologic significance than to the male, which possibly explains the preponderance of females in this series. In the symptomatology the subjects show the effects of psychogenetic influences which arise in the disorder of the personality produced by the physical disease. Barrett [11] stressed the rôle played by heredity and the prepsychotic personality in the development of this type of psychosis in pernicious anemia. Three cases are presented to illustrate this type of psychosis.

Case 3.—A native-born woman aged 52, a housewife, was transferred from another hospital because of delusions of persecution; she believed that nurses and patients about her were trying to harm her. She was abusive and yelled at the top of her voice for no apparent reason. A diagnosis of pernicious anemia had been made three years previously.

Physical Examination.—The patient was well nourished; she showed weakness in both legs, spastic paralysis of the right leg and Babinski and Hoffman reflexes on the right. The general physical, laboratory and roentgen examinations disclosed no complicating disease. The erythrocytes numbered 2,000,000 per cubic millimeter, with 11.6 Gm. of hemoglobin per hundred cubic centimeters. A stained smear revealed qualitative changes consistent with the diagnosis of addisonian anemia.

Mental State.—On admission the patient stated: "I feel all right except in my legs. I am sick three years. At the hospital they called me a crippled b———. They said my children looked like monkeys. There was a spike in the bed pan and it went up my back. The nurse had the itch and when she

23. Bender, L.: Psychoses Associated with Somatic Disease That Distort the Body Structure, Arch. Neurol. & Psychiat. **32**:1100 (Nov.) 1934.

24. Schilder, P.: Das Körperschema, Berlin, Julius Springer, 1932.

grabbed my arm she left it there too. It is on my legs, too. When the nurse washed me she made me nervous. She said she would poison me. I was there a year and a couple of months." The patient was fully oriented in all spheres and showed no impairment of memory. She talked at great length in a vindictive, abusive manner and entertained delusions of persecutions by the nurses. The condition remained unchanged, and she was removed from the hospital by relatives, against our advice, before the effects of treatment could be noted.

Comment.—In this case the psychogenic mechanism is clear. Crippled because of advanced involvement of the spinal cord, the patient projected her ideas of degradation into her environment so that she thought that the nurse called her "crippled b——" and said her children were monkeys. The paresthesias were misinterpreted and projected as being caused by external factors, viz., a spike in the bed pan and an itch contracted from a nurse. With the development of these ideas and further associations the delusions of poisoning resulted.

CASE 4.—A white housewife aged 50 was brought to the hospital by the police, to whom she had gone with the complaint that people threw acid in her mouth and talked about her at night. She believed this persecution had been instigated by her husband, from whom she had been separated for ten years. She complained of sore mouth, sore tongue and tingling and numbness of the fingers and toes for the preceding two years.

Physical Examination.—The essential findings consisted of smoothing of the tongue, absence of knee and ankle reflexes, a bilateral Babinski reflex, hyperactivity of the deep reflexes in the upper extremities, absence of vibratory sense below the knees and impairment of position sense in the toes. Examination of the blood revealed 3,800,000 red cells per cubic millimeter and 10.1 Gm. of hemoglobin per hundred cubic centimeters. Study of stained blood smears showed moderate macrocytosis. The Wassermann reactions of the blood and spinal fluid were negative. Roentgen examination of the gastro-intestinal tract revealed no abnormal condition.

Mental State.—The patient said: "I have been sick with pernicious anemia since 1925. This year people have been throwing acid around my place. Yesterday, when I was in the movies, somebody squirted something that got into my stomach, mouth and lungs. It felt like creosote. The acid burned my nose, tongue, mouth and throat. People throw some stuff around . . . formaldehyde, I think. They've been trying to harm me a long time. My husband has been trying to get rid of me. He found somebody else about 14 years old who is nicer and better than me, I suppose. He made me go to a hospital to get a puncture of my back. Since then my legs have been bad. He has people follow me around. They say things about me. If I ask them anything I get a dirty look and nasty replies. My husband comes to the house in disguise. Once he came in as a detective. He had white eyebrows and snow-white hair." Except for these profuse delusions and illusions, the patient was mentally clear and fully oriented in all spheres. She was treated with liver extract administered parenterally, which resulted in a good reticulocyte response, the red blood cell count rising to 4,200,000 per cubic millimeter in one month. There was no change in the neurologic state, and the paranoid mental picture remained the same. She was committed to a state hospital.

Comment.—The psychogenic projection mechanism of this patient's physical symptoms are apparent. The reference to persecutions by the husband are understandable when one considers that his desertion must have caused a severe blow to the ego. One can see also the development of a sense of inferiority, especially since she felt that her husband ran off with a younger, better and stronger woman. It should be noted that the degree of anemia did not play an important part in the evolution of the mental picture and that the mental picture failed to improve with improvement of the hematologic status.

CASE 5.—A white woman aged 28 was brought by her father from home. The patient stated: "They want to get my money. These people say they are my parents. I have a secret. I must tell the head doctor." The father related that she had had anemia for the past year and that in the past few months nervous symptoms had developed.

Physical Examination and Course.—The patient showed moderate pallor. There was acute glossitis, with ulcers on the sides of the tongue. The heart and lungs were normal. The blood pressure was 122 systolic and 74 diastolic. The liver and spleen were not palpable. There was paresis of the legs, with absence of knee and ankle jerks. Vibration and position sense were absent in the lower extremities, and a Babinski reflex was present bilaterally. There was retention of urine. Examination of the blood showed 2,500,000 red cells per cubic millimeter and 8.4 Gm. of hemoglobin per hundred cubic centimeters. Smears showed marked poikilocytosis, anisocytosis and oval macrocytosis. Gastric analysis showed complete absence of free acid after the injection of histamine. Treatment with liver extract administered parenterally resulted in a reticulocyte response and rise of the erythrocyte count to 3,500,000 per cubic millimeter and of the hemoglobin content to 10.3 Gm. per hundred cubic centimeters in one month. In three months the erythrocyte count was 5,200,000 and the hemoglobin content 14 Gm., a level that was maintained during the rest of the patient's stay in the hospital. The total period of observation was seven months. During this time there were two attacks of acute pyelitis. In addition, diabetes developed, caused we believe by impairment of carbohydrate tolerance resulting from an excessive amount of protein in the patient's diet.[25] Before discharge from the hospital the patient showed marked improvement. This was evident in the blood status, in the general physical state and in the neurologic condition. The right knee jerk had reappeared, the Babinski reflexes were no longer present, motor power had returned in the legs and vibration sense had improved, although position sense in the toes was still absent.

Mental State.—On admission the patient stated: "The man who calls himself my father is not my father. He wanted to get rid of me because I was sick. My parents are dead. I was kidnaped when I was a child in Russia. I am gentile, not Jewish. I am really the Czar's daughter. I got the crown. There is money coming to me—lots of it. Because I came here they treat me mean, they hurt me. I am supposed to be a high school teacher. I won eleven medals." The patient was in a restless, overtalkative state. She sought listeners and poured forth this story at a rapid rate. She was extremely elated. She evidently had delusions of wealth, power, ability and birth. Although she showed no actual

25. Jolliffe, N.; Brandaleone, H., and Most, H.: The Effect of Protein on the Carbohydrate Tolerance of Two Cases Having Combined Diabetes Mellitus and Pernicious Anemia, J. Clin. Investigation **14**:357 (May) 1935.

impairment of memory, she made small errors in statements of general information owing to carelessness and eagerness to talk about her condition. She considered herself a great actress. She blamed her family as causing her condition because they made her walk out in the rain. She said: "All men fall in love with me. I am really a blond with green eyes." Tests of memory, calculation and recall of a story were quickly and accurately performed. Some letters were found in her possession. One, to the *New York Times,* requested them to send a policeman, a lawyer and a reporter stating that she had a sensational story. Another letter was addressed to the President of the United States, asking his aid against her persecutors. She wrote that she was being called bad names in the street and over the radio—"Please, Mr. President, I am ill again because of this persecution."

When the remission induced by parenteral injections of liver extract was first manifested by a reticulocyte response, the mental state rapidly changed. She lost her delusions, and the grandiose statements and manner left her. Her explanations of her conduct varied: "Maybe I felt I was a burden to my father. I felt that way ever since I stopped working; ever since I have been ill. Before that I had supported myself; I was independent. I was born in Russia. I came here when I was 4 years old. I cried. I wanted to go back to my grandfather. He had land in Russia. He was rich and I lived with him until I came here. . . . I suppose I felt persecuted and ill treated. That's why I wrote those letters. I was reading an article by the Grand Duchess Marie. She said one of the Czar's children had been kidnaped and no trace found. That's how I got the idea."

The patient improved steadily. However, an interesting reaction occurred during a gastric analysis, the test meal for which consisted of 300 cc. of 7 per cent alcohol. She became obviously intoxicated, which released many of her inhibitions. She said: "I didn't want to live, and they saved my life, and I don't want them to save my life. I want to die, a natural death. There is nothing to fight for in life or to look forward to." Emotionally, during this period of alcoholic intoxication, depressive moods alternated with periods of forced cheerfulness. This gave a clue to the psychogenic mechanisms in this case.

We have been able to follow the patient for eighteen months since her discharge and know that she has been free from delusions and that her mental state is normal in every respect.

Comment.—This patient's condition closely resembled a paranoid type of schizophrenia. On closer analysis, however, this diagnosis is not tenable. The patient was well educated and rather gifted intellectually. She was financially independent prior to the development of the disabling involvement of the spinal cord. With the onset of the disease a feeling of inferiority developed, which the patient overcame by producing a picture of superiority. She therefore wove grandiose pictures and made boastful statements which were projected into the environment. For material she used much of her childhood experiences. She showed a tendency to blame people in her environment for the symptoms of her disease. The mental state improved concurrently with the physical condition to such an extent that all psychotic symptoms disappeared, even though the mental picture was not of an organic type. Psychotherapy was utilized concurrently with treatment with liver extract and was a factor, we believe, in the mental recovery of the

patient. In addition, the improvement in the physical state can be said to have acted psychotherapeutically by removing the basis for the symptoms. This is the only patient with pernicious anemia having a paranoid type of mental reaction in whom the mental condition improved concurrently with improvement of the condition of the blood.

AFFECTIVE REACTION

That affective reactions occur in a disease as disabling as pernicious anemia is not surprising. Mild depression, usually of short duration, is common in patients with pernicious anemia, and rarely requires treatment in a hospital for persons with mental disease. However, severe depression does occur. An affective reaction occurred in 6, or 15 per cent, of our subjects. In 5 subjects this affective reaction was a depression; in 1 a manic type of psychosis was present.

CASE 6.—A man aged 76 was brought to the hospital by his son, who stated that his father had been much depressed for the past two weeks and had attempted suicide on two occasions.

Physical Examination and Course.—The patient was pale, emaciated and senile. The tongue showed marginal smoothing. The heart was slightly enlarged to the left. The blood pressure was 110 systolic and 50 diastolic. The lungs were clear except for some moist râles at the bases. The deep reflexes were equally active. A Babinski reflex was not obtained. Position sense was intact, but there was diminution of the vibratory sense in the feet. Pain and touch sensations were impaired in stocking and glove distribution below the elbows and knees. The red blood cells numbered 700,000 per cubic millimeter, and the hemoglobin content was 4.8 Gm. per hundred cubic centimeters. A gastric analysis showed absence of free acid after the injection of histamine. The icterus index was 24. The van den Bergh reaction was of the direct delayed type. Roentgen study of the stomach and duodenum revealed no organic lesion. Liver extract was administered parenterally, and a good reticulocyte response was obtained. In fourteen days the red blood count had risen to 2,100,000, and in five weeks, to 3,900,000.

Mental State.—The patient said: "Sometimes I am half crazy. . . . I'm very weak. When I wake up in the morning it's hard to get my breath. I tried to jump out of the window last night. I wanted to end it all. I don't want to live any longer. I am old enough to go. My mind wanders all the time. I can't think of a thing for fifteen minutes." The outstanding symptom was severe depression leading to suicidal thoughts and attempts. There were also slight clouding of consciousness and mild confusion such as occurs in organic mental states. This condition cleared rapidly, the improvement paralleling the hematologic response. Within two weeks the patient was no longer depressed or suicidal but, on the contrary, was actually smiling and cheerful. The slight confusion also disappeared concomitantly. The patient's condition was so satisfactory that he was allowed to go home after six weeks in the hospital.

Comment.—This patient had a depressed state induced by the feeling of hopelessness of recovery from distressing symptoms. As the anemia improved the depression lifted. The psychogenic factors were removed by treatment of the anemia. In cases such as this relief of the anemia

improves the mental state. Mild depression accompanying other mental reactions in patients with pernicious anemia occurs frequently. It is most common in association with the paranoid states and also the organic reaction states. With the general ill health accompanying a relapse of the anemia depression is frequent. With the onset of a remission the depression usually disappears. However, for persons with depressive reactions occurring with a normal condition of the blood and especially with those deeper states of depression allied with delusions, therapy directed toward the organic disease is often of no avail. It is here that psychotherapy is important.

INDEPENDENT MENTAL STATES

Some mental diseases occurring in association with pernicious anemia may have no etiologic relationship. The conditions shown by 8 of our patients, we believe, fall in this group; the diagnoses were as follows: acute alcoholism, transitory psychosis with an episode of excitement and hallucinosis, schizophrenia, paranoid psychosis in a psychopath, cerebral vascular thrombosis, catatonia of unknown type, senile psychosis (2 cases). These psychoses, either by history or by course in the hospital, proved in our opinion to be unrelated to the pernicious anemia.

SUMMARY AND CONCLUSIONS

Mental symptoms of a degree sufficient to produce a psychosis occurred in 40, or 15.7 per cent, of 255 subjects with pernicious anemia admitted to the Bellevue Hospital in the five years from 1931 to 1935.

Pernicious anemia was found in 40, or 0.08 per cent, of 50,000 non-alcoholic persons admitted to the psychiatric division during the same period.

The mental picture of these psychoses in patients with pernicious anemia did not show any characteristic or diagnostic content.

We have classified the types of mental reaction in order of frequency as follows: an acute confusional state, a paranoid condition, an affective reaction and an organic deterioration type.

The acute confusional state occurring during a relapse of the anemia is a serious complication and should be treated by blood transfusions until the establishment of a hematologic response by specific therapy.

Technical and Occasional Notes

METHOD FOR RAPID IMPREGNATION OF MICROGLIA AND OLIGODENDROGLIA IN MATERIAL FIXED IN FORMALDEHYDE

LESTER S. KING, M.D., NEW YORK, WITH THE ASSISTANCE OF
J. ANDERSON, LONDON, ENGLAND

The need for impregnating microglia in tissue fixed in a solution of formaldehyde has led to several modifications of Hortega's original methods. I present here a further modification that has the advantages of ease, rapidity and uniformly good results.

PROCEDURE

1. Cut frozen sections of material fixed in a solution of formaldehyde at from 20 to 25 microns, receiving them in tap water to which has been added about 20 drops of ammonia per hundred cubic centimeters.

2. Transfer sections directly to a 5 per cent solution of ammonium bromide and heat in the paraffin oven at from 45 to 50 C. for from ten to fifteen minutes.

3. Transfer directly to Hortega's mixture, of equal parts of ammonia, pyridine and water, for two minutes or longer.

4. Transfer directly to a freshly made solution of sodium sulfite, from 3 to 5 per cent, for two or three minutes.

5. Transfer directly to a solution of silver carbonate, made up as follows:

5 per cent solution of sodium carbonate.....8 parts
10 per cent solution of silver nitrate.....2 parts
Strong ammonia, just sufficient to dissolve the precipitate
Distilled water .....5 parts

This is Hortega's strong solution of silver carbonate.

It is desirable to use this solution in two or three small dishes, each containing about 10 cc., leaving the sections for from twenty to thirty seconds in each dish. The total time in the solution of silver carbonate must be determined by trial but should not exceed two minutes. The sections should be manipulated in each dish with a glass rod, to secure even impregnation.

6. Reduce, without washing, in a solution of formaldehyde U. S. P. (1:100), agitating the sections by blowing, sharply and continuously, directly down on the surface of the fluid. Reduction is complete in less than a minute. The sections should be rich gray-brown. A light mouse-gray color may prove acceptable, but a tobacco-brown shade is rarely satisfactory.

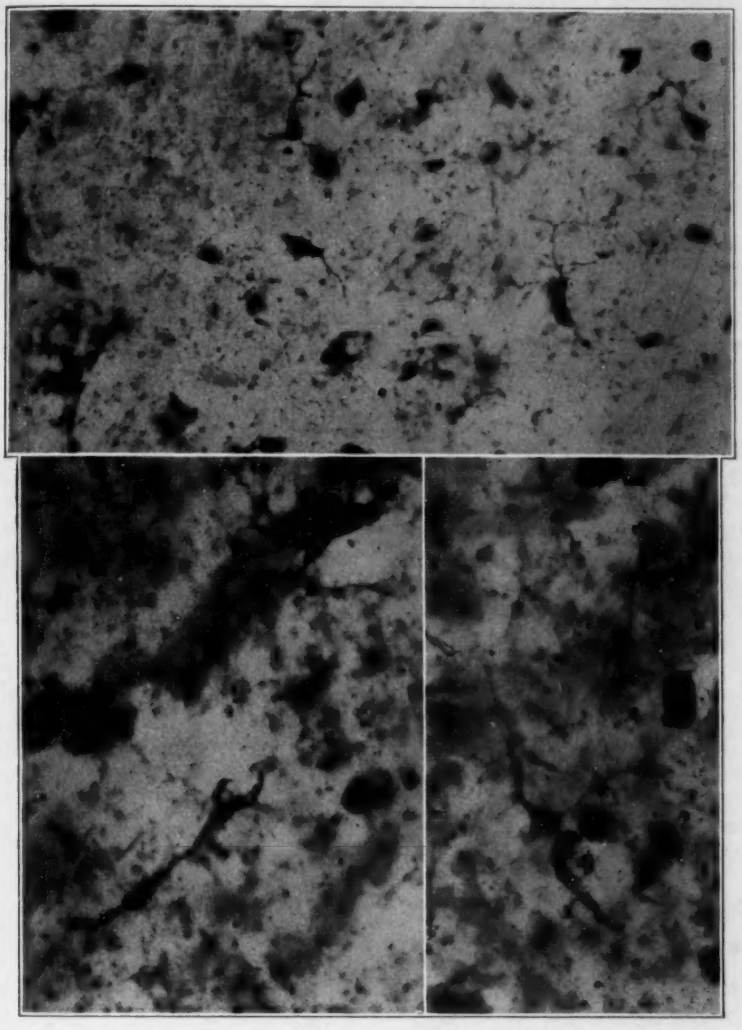
7. Wash, tone, fix and mount as in any silver impregnation.

From the pathologic laboratory of the National Hospital, Queen's Square, London; Director, Dr. J. G. Greenfield.

At the time this work was done, Dr. King was holding a Moseley Traveling Fellowship of the Harvard University Medical School.

COMMENTS

The emphasis on chemically clean glassware and water doubly distilled through glass, as recommended by some authors on technical methods, is unnecessary. Solutions should be made up with distilled water (in this laboratory only a tin-lined still is used), and sections,



These photographs are taken in a case of moderate arteriosclerosis, the tissue having been in a solution of formaldehyde for two and a half years. Three views from the cerebral cortex are shown, the upper at a magnification of 335 and the two lower at 670. The photographs are printed from unretouched negatives.

before going into any silver solution, should be washed in distilled water. Or, what is equivalent, the sections may be passed through solutions made up with distilled water. There is no necessity for washing the sections between any steps in the method outlined.

Step 3.—Successful results may be obtained in many cases without the pyridine, but in general it is deemed advisable to include it. The mixture need not be made up in a graduated vessel; the relative proportions of each constituent can be judged sufficiently accurately by eye and mixed directly in the dish.

Sept 4.—I do not measure the quantity of sodium sulfite. A few crystals, or a pinch of the anhydrous powder, suffices. It may be wise for the beginner at first to weigh out the sodium sulfite in the proportion of about 1 part to 25 parts of water. Thereafter, the approximate amount may be estimated easily without the use of scales. Inaccuracy in this respect seems to be of no importance. This solution, however, should be made up fresh each time it is to be used. All other solutions mentioned may be kept in stock.

Step 5.—The silver nitrate and the sodium carbonate should be of the highest grade of purity obtainable. Equally good results have been obtained with either the crystalline or the anhydrous sodium carbonate, a 5 per cent solution of each being used, regardless of the difference in molecular weights. The solution of silver carbonate should be made up strong. If it stains too quickly to allow even impregnation, it may be diluted with water about a third. The dilution should be made in the staining dish, not in the stock bottle.

It should be emphasized once more that the best results are obtained if the sections are passed rapidly through three, or even four, staining dishes, in fairly rapid succession.

The solution of silver carbonate is not the only ammoniacal silver solution that gives successful results. The following solution may also be used: To any given amount of a 10 per cent solution of silver nitrate (as 15 cc.), strong ammonia is added until the precipitate formed just dissolves. If an excess of ammonia is inadvertently used, more silver nitrate may be added and the excess precipitate just dissolved. The resulting solution should be diluted with about the same quantity of distilled water. This form of ammoniacal silver gives somewhat sharper and more contrasting impregnations than the silver carbonate, but the differentiation is not always as delicate. It is, however, strongly recommended as an alternative to silver carbonate. The use of sodium hydroxide as the initial alkali, as in the Bielschowsky or DeFano solution, cannot be recommended. The microglia may stain, but incompletely and with little selectivity.

The directions given may be modified over a wide range, in many directions. Either step 3 or step 4 may be omitted, and with tissue from cases of dementia paralytica, the preliminary ammonium bromide may even be dispensed with, and yet passable results may be given. The strengths of the solutions in steps 2, 3, 4 and 5, as well as the times in steps 2, 3 and 4, may be varied within the widest limits, and yet passable impregnations may result. However, in difficult and refractory tissue in this laboratory, success has been obtained only with the directions given. With this method I have had consistently good results in impregnating both microglia and oligodendroglia, in pathologic and in normal material.

For those desirous of practicing this method, it is recommended that the first trials be made on brain tissue from a patient with dementia paralytica, which is extremely easy to impregnate.

CONTINUOUS RECORDS OF SYSTOLIC AND DIASTOLIC BLOOD PRESSURE

CHESTER W. DARROW, PH.D., CHICAGO

Lack of a satisfactory method for recording continuous systolic and diastolic blood pressures without puncture of an artery has caused resort to various substitutes. Several methods have been devised to facilitate successive absolute readings by graphic or auscultatory procedures. These methods are without exception too slow to catch the more rapid fluctuations in pressure attending change in stimulating conditions. Furthermore, the stimulation of the patient by the repeated inflation and release of pressure which these methods entail is often itself more effective of change in blood pressure than the special physiologic or psychologic conditions which it is desired to investigate.

Mosso[1] developed a method for obtaining continuous graphic records of relative changes in blood pressure by recording the fluctuations in the volume of the fingers when under pressure maintained in a glovelike arrangement by a column of mercury. Erlanger[2] devised a method for recording continuously fluctuations in the volume of a limb by means of a sphygmomanometer. The method has had wide application, because it, like that of Mosso, provides indication of the fleeting, but none the less important, fluctuations attending stimulation.[3] These methods and others involving essentially the same principles are, however, unsatisfactory in the sense that the changes thus recorded are indications of only relative change and provide no adequate means for determining the absolute variation, expressed in millimeters of mercury. Furthermore, vasomotor changes under the cuff may complicate the pressure record, and the mode of application of the blood pressure cuff, the degree of its inflation and the size of the limb to which it is applied each may affect the magnitude of the changes and prevent satisfactory comparison of results for different persons and may even interfere with comparison of results for the same person at different times. Although under certain conditions such records may follow the diastolic level closely, readings of the blood pressure level in millimeters of mercury may be only roughly approximated by the method.

Studies from the Institute for Juvenile Research, Paul L. Schroeder, Director, series C, no. 278.

1. Mosso, A.: Sphygmomanomètre pour mesurer la pression du sang, Arch. ital. de biol. **23**:177, 1895.

2. Erlanger, J.: A New Instrument for Determining the Minimum and Maximum Blood Pressures in Man, Johns Hopkins Hosp. Rep. **12**:53, 1904; On the Physiology of Heart Block in Mammals with Especial Reference to the Causation of Stokes-Adams Disease, J. Exper. Med. **7**:676, 1905.

3. Darrow, C. W.: Electrical and Circulatory Responses to Brief Sensory and Ideational Stimuli, J. Exper. Psychol. **12**:267, 1929. Darrow, C. W., and Solomon, A. P.: Galvanic Skin Reflex and Blood Pressure Reactions in Psychotic States, Arch. Neurol. & Psychiat. **32**:273 (Aug.) 1934.

Two methods, at least partially satisfactory, for obtaining continuous records of blood pressure expressed in absolute units (millimeters of mercury) have been described in the literature. Kolls [4] described an apparatus by which continuous records of systolic blood pressure may be obtained by means of a double blood pressure cuff, the lower chamber of which can be cut off manually from the remainder of the system and used to provide mechanical "auscultation" of pulsations which are able to pass the upper cuff. Pulsations which reach the lower cuff are made to break an electrical contact, thereby operating a relay controlling a valve, which then shuts off the inflow of air and permits the outflow from the upper cuff. With a rise in pressure within the upper cuff and the cessation of pulsations in the lower cuff, the valve again permits the inflow and cuts off the outflow of air in the upper cuff. Thus, the pressure in the upper cuff is continuously maintained at approximately the systolic level, and this pressure may be recorded graphically. The manipulation of the stopcock separating the upper from the lower cuff is determined by the subject's report of sensations of pulsation in the arm.

Recently, Kronfeld, Müller and Reiner [5] have reported the results of a study of changes in the continuous absolute blood pressure, as recorded by an apparatus devised and patented by K. Lange. The mechanical details of the device are not given, but the principle of operation of the apparatus is described. For recording diastolic pressure, air is permitted to flow from a pressure tank into an arm cuff until the pressure is sufficient to cut off the top of the pulse waves received at the wrist by means of a tambour. An increase above diastolic pressure, which increases the sound in the stethoscope, also affects the pulsations of the tambour and, by an undescribed mechanism, cuts off the flow of air from the tank; a slow leak then permits the pressure to fall until the pulse at the wrist again becomes normal and air again is permitted to flow in from the tank. Systolic pressure is recorded by changing the adjustment of the apparatus so that the air supply from the tank is cut off only when the pulse wave ceases to reach the tambour on the wrist. The physiologic principles involved are undoubtedly correct. The mechanism of its operation cannot be discussed, for it has not been described. The authors indicated, however, that there is difficulty in ascertaining diastolic pressure with the device and that a pressure considerably below the diastolic level is much more satisfactory to record. The published sample records from the device suggest that there may be considerable irregularity in its operation.

The apparatus of my construction to be described is the result of efforts extending over ten years to provide an absolute quantitative value for the continuous blood pressure record. Briefly, the device consists of (1) two blood pressure cuffs, or of a single cuff with two chambers, one above the other, which may be wrapped around the arm or leg; (2) a differential tambour for detecting electrically the differential effect of the pulse waves from the respective cuffs, (3) a capillary oscillator containing a drop of liquid for observing the differential effect visually, (4) an electromagnetic valve for adjusting automatically the pressure in the system, (5) a suitable manometer for indicating or recording pressure and (6) a "gang" of three four way stopcocks by which the movement of a single lever arranges the system for recording either diastolic or systolic pressure.

---

4. Kolls, R.: Continuous Blood Pressure Tracings in Man: An Apparatus, J. Pharmacol. & Exper. Therap. **15**:433, 1920.

5. Kronfeld, A.; Müller, A., and Reiner, R. C.: Untersuchungen mit dem Autotonographen, Ztschr. f. d. ges. Neurol. u. Psychiat. **145**:62, 1933.

The details of the complete mechanism are schematically represented in figure 1*A*. Simplified arrangements recording, respectively, only diastolic or systolic pressure are presented in figure 1*B*. For recording diastolic pressure, air from the pump, *P*, and reservoir *R* passes through a four way stopcock (fig. 1*A*) to enter the system through the capillary tube ("leak") *L*, from whence it reaches the cuffs, *A* and *B*, through the respective capillary tubes *L'* and *L"* and the by-pass valve, *V'*. Below diastolic level, when the pressure in the upper cuff

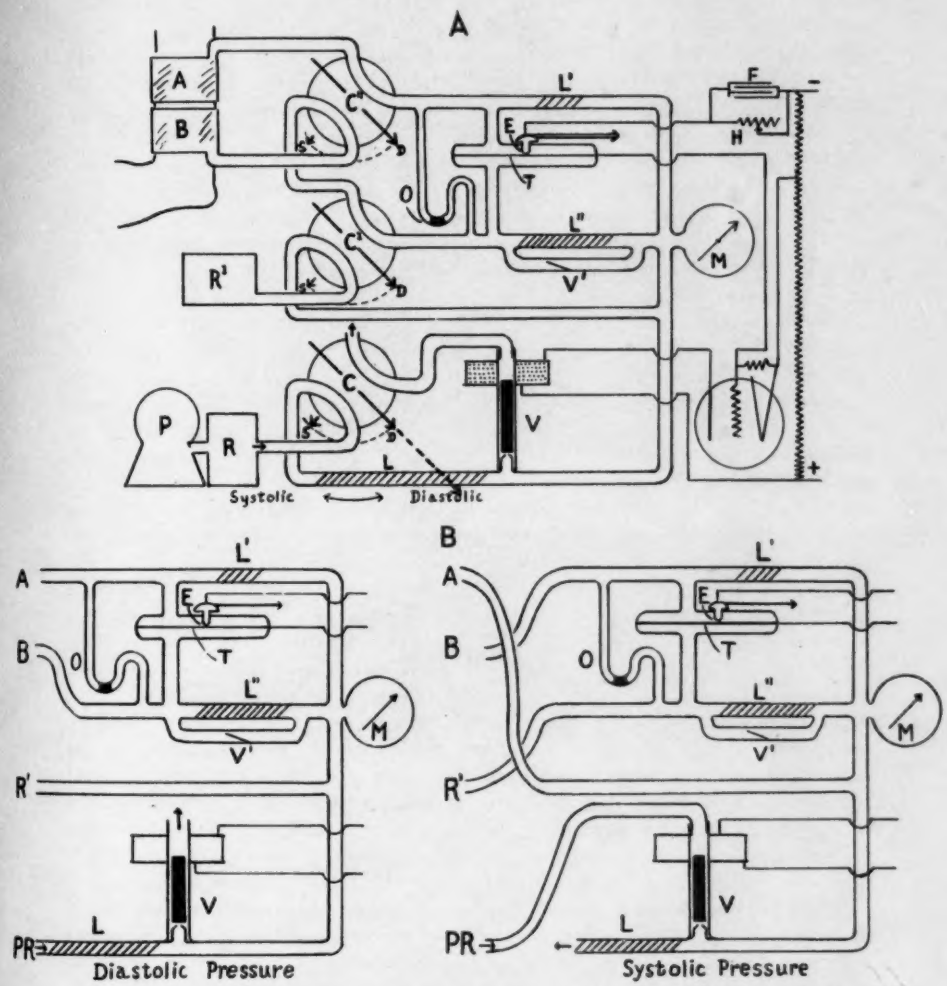


Fig. 1.—Schematic drawings of the apparatus for the recording of continuous blood pressures. *A*, indicates the upper blood pressure cuff; *B*, the lower cuff; *C*, *C'* and *C"*, the "gang" of four way stopcocks, adjusted at *D* for diastolic pressure and at *S* for systolic pressure; *E*, an adjustable contact; *F*, a condenser; *H*, a variable high resistance; *L*, *L'* and *L"*, capillary "leaks"; *M*, a spring manometer; *O*, an oscillation indicator; *R* and *R'*, air reservoirs; *T*, a differential tambour; *V*, an electropneumatic valve, and *V'* a by-pass valve.

does not interfere with the passage of the pulse waves, the impulses transmitted from the lower cuff may be observed in the oscillator to be stronger than those from the upper cuff, and as a result, the contact at *E* remains unbroken. When, however, air has entered the system sufficient for the pressure in cuff *A* to cut off a portion of the pulse wave to cuff *B*, the pulse wave transmitted from *A*, as may be seen in the oscillator, precedes or becomes stronger than that from *B*, and the tambour, *T*, is momentarily forced downward with each pulse wave, thus breaking the electrical contact, *E*, and opening the magnetically operated valve, *V* (by means of a vacuum tube relay). This permits the momentary escape of air with each pulse wave and reduces the pressure until that in cuff *A* no longer cuts off the peak of the pulse waves reaching cuff *B*. By observation of the oscillator, the contact, *E*, may be adjusted for each person examined, so that pressure is automatically maintained just sufficient for observable waves to appear from the upper cuff. Thus, the pressure in the system, as indicated by the manometer, *M*, is made to approximate the fluctuations of the diastolic pressure, with only such delay as may be required for the device to reach equilibrium with the fluctuating arterial pressure. The use of a shorter capillary leak at *L'* than at *L"*, and a valve, *V'*, giving a one way by-pass around *L"*, pneumatically maintains the electrical contact at *E* during moments of rapid decrease or increase of pressure and gives stability to the system.

For continuous records of systolic pressure, a single lever connected to all three stopcocks, *C*, *C'* and *C"* (fig. 1 *A*), is moved through 90 degrees. This adjustment rearranges the system to correspond with that shown for systolic pressure in figure 1 *B*, so that air now enters by the electropneumatic valve, *V*, and escapes through the capillary leak *L*. This adjustment also connects the chamber above the tambour, *T*, with the lower blood pressure cuff, instead of with the upper cuff, and connects the chamber below the tambour, *T*, with an air chamber *R'* not directly affected by the pulse waves. By this arrangement pulse waves which reach the lower cuff will break the electrical contact, *E*, thereby momentarily opening the air valve *V* and increasing the pressure in the system. This will be repeated with each pulse wave until the pressure in the upper cuff is sufficient to cut off completely the pulse waves to the lower cuff. The point at which this occurs is the level of systolic pressure. Operation of the leak *L* tends to bring the pressure down to the point where the pulse waves again pass the upper cuff.

The use of a vacuum tube relay in this device provides great sensitivity to slight changes in contact at *E* and offers a means by which the degree and duration of opening of the pneumatic valve are determined by the magnitude of the differential between pulse waves from the upper and the lower cuff. This is accomplished by the fact that the degree of opening of the valve *V* is determined by the charge on the condenser, *F*, which in turn is controlled by the duration of the opening of the contact, *E*. A variable high resistance, *H*, provides a means of obtaining an optimal adjustment of the rate of charge.

The electromagnetically operated valve, *V*, consists of a pipet, on the tip of which rests a rubber-tipped iron plunger moving freely within a glass tube, which is part of the air-conducting system. An electromagnetic coil of several thousand turns surrounds the glass tube at the level of the upper end of the iron plunger and lifts the plunger within the tube on the passage of a suitable electric current. The effectiveness of the solenoid is enhanced by placing the tube and enclosed plunger in a strong magnetic field between two permanent magnets.

This apparatus may be employed to give readings either from the arm or from the leg. Readings from the leg, with the cuffs applied above the ankle and the patient in a reclining position (the cuff at the level of the heart), have the advantage of offering a minimum of discomfort during extended records. Appli-

cation of the cuffs to the wrist supported at the level of the heart also gives less discomfort than application to the upper portion of the arm. Diastolic pressure in the cuff is, of course, the cause of less discomfort than systolic pressure. For records of both the systolic and the diastolic pressure two machines have been employed and records obtained from the two legs. The systolic pressure may be obtained first from one leg or wrist and then from the other, so that the period of interference with circulation in any one region may be minimal.

To record the systolic and the diastolic pressure simultaneously, as shown in figure 2, we employed the shadows cast, respectively, by a series of spokes and semitransparent celluloid vanes attached to the pointers of two Tycos dial manometers. The spokes are spaced in scale units 20 mm. of mercury apart, and the vanes are 20 mm. of mercury wide, with a space of 20 millimeters of mercury between them. The spokes and vanes are so placed that the 20 mm. divisions cast shadows approximately 20 mm. apart on the photographic record. The moving scale thus provided is read relative to zero on the record, and since one sub-

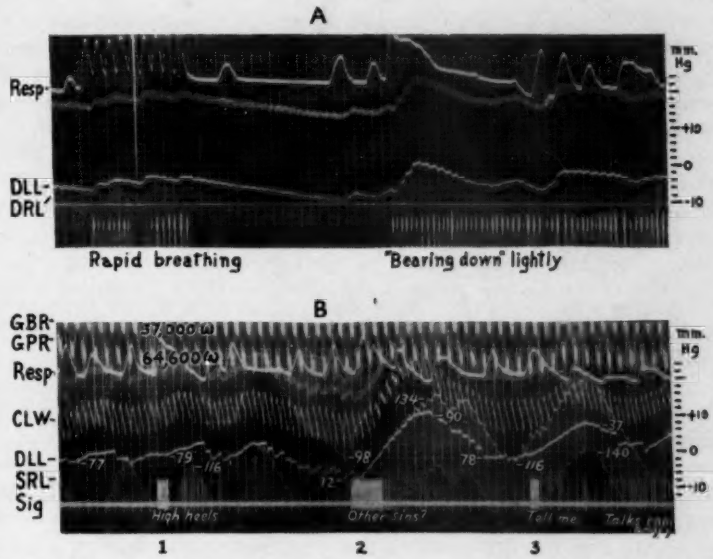


Fig. 2.—Tracings of diastolic and systolic pressures taken simultaneously. *A*, independently recorded parallel diastolic pressures in a normal person. *DLL* (the white line) indicates the diastolic pressure in the left leg, and *DRL* (edge of the transparent shadow), the diastolic pressure in the right leg. The vertical white lines are second marks. *B*, reactions of a psychotic patient in a psychiatric interview. The broken lines *GBR* and *GPR* indicate the galvanic cutaneous reflex from the back and the palm of the right hand, respectively; *Resp*, respiration; *CLW*, continuous sphygmomanometric pressure in the left wrist; *DLL*, diastolic pressure in the left leg; *SRL*, systolic pressure in the right leg; *Sig*, signal marks, and *1*, *2* and *3*, questions by Dr. A. P. Solomon: *1*, "Do you wear high-heeled shoes every day?"; *2*, "What other sins did you commit that were serious?" and *3*, "Tell me what they are."

The white line recording diastolic pressure indicates 80 mm. of mercury, when it is level with zero on the scale at the right; the upper edge of the transparent shadow recording systolic pressure, 120 mm. of mercury, the lower edge of the same shadow, 140 mm. of mercury, when level with zero.

division of the scale moves onto the record as another moves off, it affords a uniform sensitivity to fluctuation throughout the entire pressure range, without manual adjustment.

The apparatus has not as yet been developed for use with animals, although there seems to be no reason that it may not eventually be made sufficiently sensitive to record from the leg of a dog or a cat. Without the employment of animals there are three obvious methods of checking this apparatus in human patients in whom puncture of an artery is objectionable: (1) comparison of simultaneous records obtained by different machines on the same person; (2) observation of the degree of parallelism between the records obtained with this machine and those obtained by the method of continuous relative (sphygmomanometric) pressure, and (3) determination of the degree of correspondence obtainable between recorded pressures and intermittent pressures read by auscultation. The parallelism of two simultaneous blood pressure records obtained from different legs by different machines is illustrated in figure *2 A*. The relation of the continuous systolic and diastolic readings from the two legs (with the subject reclining) to continuous relative changes recorded by a sphygmomanometer cuff on the left wrist is shown in figure *2 B*. Auscultatory readings with a mercury manometer, taken occasionally during recording of the reactions of normal and psychotic persons of different ages and different levels of blood pressure, have shown good correspondence with the measures obtained with this apparatus. In a reactive subject under varied stimulation for whom the record was accompanied by auscultatory readings throughout a period of thirty minutes, the average difference between the recorded and the observed pressure was 2.9 ± 2.1 mm. of mercury in the case of the diastolic pressures and 3.8 ± 4.8 mm. in the case of the systolic pressures. The Pearson coefficients of correlation, r, between the two were 0.946 ± 0.014 for the diastolic pressures and 0.865 ± 0.033 for the systolic pressures.

Although the preceding figures indicate the absence of exact correspondence with auscultatory readings, it is obvious that when blood pressure is subject to rapid variation, differences between an auscultation reading and a recorded pressure may be due in part to the time elapsing between the moment of observation and the report and signaling of the observed pressure on the record. Furthermore, it is obvious that momentary extremes of fluctuation, especially in the case of systolic pressure, would only infrequently be caught by the auscultatory method. When actual error contributes to the discrepancy, it ordinarily may as reasonably be attributed to fault of observation as to defect in the instrumental record.

Studies now under way with this apparatus provide a quantitative evaluation of the recognized effect of "disturbing" or "conflict-inducing" ideational stimuli on blood pressure.[6] The marked influence of strong mental effort, such as is involved when difficult mental multiplications are done against time, also is evident. The greater absolute effect of such ideational stimuli on the systolic and the pulse pressure than on the diastolic pressure is evident, but significant increases in the diastolic pressure are also generally shown (fig. 2). Marked individual differences have appeared, apparently correlated with the facility with which the subject is aroused to defensive and aggressive attitudes involving presumed activity of the sympathico-adrenal system.

6. Darrow, C. W.: Emotion as Relative Functional Decortication: The Role of Conflict, Psychol. Rev. **42**:566, 1935.

SPECIAL ARTICLES

FUNCTIONAL DETERMINANTS OF CEREBRAL LOCALIZATION

K. S. LASHLEY, PH.D., D.Sc.
BOSTON

Since the pioneer work of Broca and of Fritsch and Hitzig, there has been a steady accumulation of evidence for the anatomic and functional specialization of different cerebral areas. Diversities of cortical structure revealed by myelino-architectural and cyto-architectural studies have been correlated with differences in subcortical connections and with consistent and characteristic symptoms of defect following local injuries. The principal sensory and motor areas have been delimited, and the problem of cerebral localization has become one of the degree of specialization within cyto-architectural areas, of the nature of the functional disturbances following various types of injury and of the mechanisms of organization.

Behind these questions of detail and interpretation there remains, however, the problem of the functional significance of all localization. The basis of localization of function within the nervous system is apparently the grouping of cells of similar function within more or less isolated nuclei or fields. The fundamental problem for the student of localization is to discover what functions are served by this grouping and isolation. What activities of the cells are favored by such an arrangement? What functions does it permit that could not be carried out if the cells were uniformly distributed throughout the system? Has localization or gross anatomic differentiation any functional significance whatever?

The answers to these questions are not so self-evident as is often assumed. Neither current theories of the physiology of nervous integration nor the observed phenomena of anatomic and functional specialization provide an obvious reason for the particular functional divisions of the cortex which must be deduced from symptoms of local injury. Increasing knowledge of the facts of cerebral localization has only emphasized ignorance of the real reason for any gross localization whatever.

From the Department of Psychology, Harvard University.

Read before the Boston Society of Psychiatry and Neurology, March 19, 1936.

MENTALISTIC INTERPRETATIONS OF LOCALIZATION

For early investigators it was sufficient to regard the separate cerebral areas as the seat of distinct mental functions. Descartes had described the brain as a sort of filing cabinet in which the memories of the soul are stored. Phrenologists followed the facultative psychology of their time and found it natural that a thoroughly compartmentalized mind should have its activities distributed in space in accordance with a logical classification of its functions. Fritsch and Hitzig [1] described the stimulable cortex as the "place of entry of single psychic functions into matter," and many, even recent, authors have followed their lead in mentalistic interpretation. In such dualistic systems localization of functions could be regarded as a necessary consequence of the organization of mind, and the question of the functional value of anatomic specialization scarcely arose.

The error of the phrenologists lay in the assumption that a classification of mental traits, arrived at by logical analysis of behavior, reveals functions which must necessarily have a separate cerebral localization. More recent clinical studies have only in part avoided this fallacy. They have not assumed that all supposed psychologic entities must have separate localization but have sought the reason for localization in mental organization. Wernicke and later students of aphasia, notably Pick,[2] have tried to analyze the language function in terms of logical categories which would correspond to the clinical types of aphasia. The explanation of localization implied is still in terms of the products of cerebral activity rather than terms of the nature of the cerebral mechanisms themselves.

Perhaps this is only a methodologic dualism necessary in any pioneer study. Insight into the organization of behavior may be gained by study of its disorganization following organic lesions, and something of the mechanism of cerebral physiologic activity may be inferred from the organization of behavior. Explanations of cerebral activity, however, cannot satisfactorily be cast in mentalistic or behavioral terms. The conclusion that two functions the separate localization of which has been determined clinically have disparate cerebral loci because they are recognizable as distinct functions in behavior is merely a circular argument.

An approach to the problem of localization from the standpoint of psychologic functions leads to a hopeless tangle of contradictions. The projection areas for the various sense modalities are anatomically separate; yet it does not follow that spatial separation is essential for

1. Fritsch, G., and Hitzig, E.: Ueber die elektrische Erregbarkeit des Grosshirns, Arch. f. Anat., Physiol. u. wissensch. Med., 1870, pp. 300-332.

2. Pick, A.: Die agrammatischen Sprachstörungen, Berlin, Julius Springer, 1913.

differential sensory reactions, since some of the finest discriminations, such as between odors, are certainly not dependent on gross anatomic separation of receptive centers. The discrimination of qualities or "dimensions" within any sense modality does not seem to involve any processes psychologically different from those in discrimination between modalities, so that one cannot correlate the discriminative process in general with the anatomic separation of the excitations distinguished or appeal to discrimination to account for localization.

Psychologic unity is also not a criterion of localization. The motor processes of "voluntary movement" seem psychologically quite unitary. The various disturbances arising from lesions to the cortical motor and premotor areas, the basal nuclei and the cerebellum indicate, however, that the motor function is a physiologic complex the components of which are unintelligible in terms of psychologic analysis. Thus, a function which from an introspective or a behavioristic standpoint is completely integrated and unanalyzable turns out, when its pathologic aspect is studied, to be controlled by widely scattered loci contributing quite diverse elements to the whole.

Much stress has been laid on the discrete localization of memory traces, but nothing is more evident in the clinical and experimental literature than that individual memories are never destroyed by small lesions. The clinical picture of amnesia is one of a greater or less weakening of all memories of a general class from any lesion which is at all effective; the experimental picture is that of the preservation by any part of a functional area of all memory traces with which the whole is concerned.[3] The development of conditioned reflex paths or the formation of memory traces is not the basis of observed localizations.

The evidence for the parallel development of intelligence and the "association areas" provides no reason for the anatomic separation of such areas. The single sensory projection area can mediate functions of the same psychologic character as those which are classed as intelligent. Thus, Frank and I[4] have found that the discrimination of visual patterns by the rat is not disturbed by lesions in any cerebral area except the primary visual centers. Such discriminations involve processes of differentiation and organization which are not definably

3. Lashley, K. S.: (*a*) Nervous Mechanisms in Learning, in Murchison, C. A.: Foundations of Experimental Psychology, Worcester, Mass., Clark University Press, 1929, pp. 524-563; (*b*) The Mechanism of Vision: XII. The Nervous Structures Concerned in the Acquisition and Retention of Habits Based on Reactions to Light, Comparative Psychology Monograph, serial no. 52, Baltimore, Johns Hopkins Press, 1935, vol. 11, pt. 2, pp. 43-79.

4. Lashley, K. S., and Frank, M.: The Mechanism of Vision: X. Postoperative Disturbances of Habits Based on Detail Vision in Rat After Lesions in Cerebral Visual Areas, J. Comp. Psychol. **17**:355-380, 1934.

different from the generalizations and abstractions involved in the "higher" intellectual processes. The early controversy concerning the functions of the "associative areas," in which Munk maintained that the interaction of sensory fields is sufficient for the intellectual functions while Hitzig stressed the need for higher correlating centers, at least demonstrated the lack of any a priori reason for expecting the development of separate "intellectual" centers.

These illustrations are typical of what is found in any attempt to relate localization of function to psychologic or behavior categories. Functions which seem unitary in behavior are broken up by local lesions, and functions which seem markedly diverse are carried out within the same anatomically homogeneous field. Whenever separate localization of two psychologic entities is established, giving an apparently valid reason for spatial separation, a parallel and equally impressive case can be found in which there is not separate localization.

LOCALIZATION AND GENERAL THEORIES OF INTEGRATION

The reflex or connectionist theories of nervous integration, which assume that activity is determined by the transmission of impulses over relatively isolated neural paths through associative connections built up in learning, would be equally applicable if no gross localization existed. In a telephone system convenience of administration and economy of construction are attained by a system of local exchanges, but the working of the exchanges is not dependent on a geographic arrangement of the switchboards. The extreme connectionist theory, represented by behaviorism, asserts that the formation of new associative connections is independent of any innate structural organization of the cortex and therefore implies the absence of localization except as built up by chance associative connections. At most, therefore, the connectionist theories suggest that economy in length of reflex arcs may be effected by localization, but they give no reason for such detailed topographic arrangements as appear in the striate area or the central gyrus, nor do they give the least hint of a reason for such dissociations of function as are seen in the aphasias or agnosias.

The theory of the development of adjacent excitatory and inhibitory centers, irradiation between which determines balance of activity and the character of integration, as proposed by Pavlov,[5] might provide a reason for the spatial separation of functional mechanisms. Clinical and experimental data on localization, however, give no indication that this is the actual basis of structural differentiation. On the contrary,

5. Pavlov, I. P.: Die Charackteristik der Rindenmasse der Grossehirnhemisphären, vom Standpunkte der Erregbarkeitsveränderungen ihrer einzelnen Punkte, Schweiz. Arch. f. Neurol. u. Psychiat. **13**:568-574, 1923.

studies of spinal reflexes and of the motor cortex indicate that excitation and inhibition may be originated within the same center. The major anatomic fields of the cortex are clearly not interrelated on any principles of reciprocal innervation, nor did Pavlov himself suggest any such relation.

Other general theories of neural integration, resonance theories, doctrines of cortical dominance and the like are too vague to suggest anything definite concerning the basis of cerebral localization.

MORPHOGENIC BASIS OF LOCALIZATION

The aggregation of neurons having similar functions in distinct areas or nuclei does not in itself justify an interpretation of structure in terms of adaptation, any more than does the distribution of pigment on the skin of a piebald animal. Both may be the product of developmental forces, important for the formation of the embryo but without significance in the behavior of the differentiated animal. The function of the cells may be deduced from their position and connections, but their position is not therefore a necessary consequence of their function. Some part of the structural diversity of the nervous system may well be an accidental product of the mechanism of embryonic development. By the general principles of neurobiotaxis, neuroblasts developing simultaneously in a given region are subject to the same developmental forces and will send their axons to a common field. Thus, local groups of cells having similar functional connections will arise; yet the fact of their aggregation and the consequent "localization of function" may be entirely without significance for the integrative processes in which they participate.

For example, the regular arrangement of ascending fibers in the dorsal funiculus of the spinal cord seems to be determined by the time at which developing axons reach a given level, the later arrivals from lower levels displacing laterally those established earlier. Continuation of this arrangement into the nucleus gracilis and nucleus cuneatus would give a definite "localization of function," yet would not justify the conclusion that the physiologic activity of these nuclei is dependent in any way on the spatial arrangement.

How much of the structural differentiation of the nervous system is ascribable to such developmental processes and is irrelevant for behavior cannot be determined from the anatomic facts alone. The common occurrence of vestigial structures in other parts of the body suggests that the arrangement of many of the major divisions of the mammalian nervous system may represent only a recapitulation of their phylogenetic history. The separation of the sensory fields of the cortex may have no further significance than that the neuroblasts in the

thalamic nuclei differentiate at different times; the association areas may be distinct from the projection fields only because they represent masses of nerve tissue of later evolutionary origin. Thus, the mere existence of specialized regions in the brain is not conclusive evidence that the specialization is necessary or important for the integrative functions. On anatomic grounds alone there is no assurance that cerebral localization is anything but an accident of growth.

I do not wish to overemphasize this point. The vast majority of structural arrangements in the nervous system, especially among the lower nuclei and tracts, look as if they must have some functional value. But it is important to realize that this functional value is accepted largely as a matter of faith and that there are no certain anatomic or behavioral principles by which the significance of any particular instance of localization may be judged.

FUNCTIONAL VALUE OF CEREBRAL LOCALIZATION

The most impressive evidence that the differentiation of cerebral fields is more than a chance product of developmental mechanics comes from cases in which nature seems to be at great pains to restore an order which has been lost at some earlier developmental stage. In the visual system, for example, the orderly arrangement of the fibers from the retinal elements is partly or completely lost in the optic nerve and chiasm, to be reconstituted within the lateral geniculate nuclei, in a three dimensional system.[6] Again, between the lateral geniculate nucleus and the area striata the fibers are confused in the optic radiation, and the order is again restored, this time in two dimensions, in the visual cortex.[7] The developmental history of the visual system is such that simple principles of displacement, such as apply to the dorsal spinal funiculus, will not account for the distribution of fibers. The cortical retina becomes intelligible only on the assumption that the projection of the retina on the cerebral surface is essential for some phase of visual reaction.

What is the nature of the nervous processes which demand such isolated mechanisms or depend on the topographic reproduction of sensory surfaces in the cerebrum? It has been seen that interpretations in terms of behavioral resultants lead to confusion. The answer must be sought in the nature of the physiologic mechanisms themselves. Recent

6. Sjaff, M., and Zeeman, W. P. C.: Ueber den Faserverlauf in der Netzhaut und im Sehnerven beim Kaninchen, Arch. f. Ophth. **114**:192-211, 1924. Lashley, K. S.: The Mechanism of Vision: VII. The Projection of the Retina upon the Primary Optic Centers in the Rat, J. Comp. Neurol. **59**:341-373, 1934.

7. Lashley, K. S.: The Mechanism of Vision: VIII. The Projection of the Retina upon the Cerebral Cortex of the Rat, J. Comp. Neurol. **60**:57-79, 1934.

experimental work presents some clues as to the reasons for physiologic isolation and for the separate localization of such functions as are actually dissociated by lesions. Two types of nervous function stand out conspicuously as characteristic of the activities of different centers and suggest the principle that separate localization of functions is determined by the existence of diverse kinds of integrative mechanism which cannot function in the same nerve field without interference. The assumption of such incompatibility or mutual exclusion of physiologic processes is consistent with many facts of cerebral localization.

Mechanisms Which Regulate Intensity of Response.—The studies of Sherrington and his co-workers on the properties of the motoneuron pool defined the activities of a center which is primarily concerned with the regulation of the intensity of response.[8] The mechanisms suggested for facilitation, recruitment and inhibition depend on the aggregation of neurons of like function within a homogeneous field, within which there is overlap of axon terminations. Summation within the subliminal fringe (the overlapping fields of different axons) contributes importantly to the gradation of intensity of the discharge from the motoneuron pool.

Such a mechanism is well adapted for gradation in intensity of activity, but it would work imperfectly in maintaining separate representation of very small functional units, such as are involved in foveal vision or in tactile discrimination. The efficiency of the system for gradation of intensities is dependent on the close anatomic grouping of cells with common function and on the extent of the subliminal fringes, and this is incompatible with cell to cell correspondences.

Regulation of Spatial Orientation.—If one examines the chief cerebral projection areas with respect to the degree of subordinate localization within them, as indicated by the diversity of symptoms produced by small focal lesions, one finds that the visual, tactile and motor regions have a high degree of internal specificity, whereas there is little or no evidence of subordinate localization within the olfactory and gustatory fields. (The position of the auditory area in this grouping is uncertain. I have found some separate projection of different parts of the medial geniculate nucleus but no such detail of anatomic differentiation as prevails in the visual and tactile systems.) Reactions mediated by the visual and tactile areas are primarily spatial; that is, the reactions are to the relative spatial position of points on the receptive surfaces. The motor region is concerned with the selective spatial distribution of excitations to different muscle groups. There is a striking contrast

8. Sherrington, C. S.: Some Functional Problems Attaching to Convergence, Proc. Roy. Soc., London, s.B **105**:332-362, 1929; Quantitative Management of Contraction in Lowest Level Co-Ordination, Brain **54**:1-28, 1931.

between these areas which are most directly concerned with spatial reactions and other projection and association areas with respect to the degree of subordinate differentiation within them. This suggests that reproduction of the topography of the sensory surface on the surface of the cortex is somehow important for orienting reactions.

Little is known of the actual mechanisms of such reactions. They consist of the translation of a pattern of sensory excitement into a pattern of movement with reference to bodily posture. Studies of perception, especially in vision, have defined some of the properties of the mechanism. It is clear that no simple connectionist hypothesis will account for the facts of functional equivalence of parts and for the relational character of the adequate stimuli. The system has the characteristics of a field of interacting forces, as illustrated by interacting magnetic fields or overlapping diffusion gradients. Motor reactions are determined by the distribution of excitations within the field, irrespective of the particular neurons excited.[9]

When one tries to imagine a mechanism for this type of reaction, it is necessary to postulate two fields of force so related that a pattern of tensions or stresses within one field (a sensory area) will induce a different, but constant, pattern in the other (motor zone).[10] Rashevsky has approached this problem from the standpoint of physical systems and has shown that such patterns of excitation as form or contour have certain simple mathematical properties which differentiate each from every other and that postulated physical correlates of the mathematical properties will exhibit relations corresponding to the phenomena of behavior.[11] I have proposed a theory of interference effects of radiated excitations to account for the phenomena of sensory equivalence,[12] and the "resonance" hypothesis of Weiss suggests a still different mechanism.[13] None of the hypotheses gives a satisfactory solution of the problem at present, but all imply a type of organization between cortical systems different from the organization revealed by studies of the motoneuron pool.

Evidence for the Anatomic Separation of Mechanisms for Spatial Adjustments and Regulation of Intensity.—Thus, the little that is known

9. Lashley, K. S.: Basic Neural Mechanisms in Behavior, Psychol. Rev. **37**: 1-24, 1930.

10. Köhler, W.: Die physischen Gestalten in Ruhe und im stationären Zustand, Erlangen, Weltkreisverlag, 1920, pp. x and 263.

11. Rashevsky, N.: Physico-Mathematical Aspects of the Gestalt-Problem, in Sheen, F. J.: Philosophy of Science, Milwaukee, The Bruce Publishing Company, 1934, vol. 1, pp. 409-419.

12. Lashley, K. S.: Mass Action in Cerebral Function, Science **73**:245-254 (March 6) 1931.

13. Weiss, P.: Das Resonanzprinzip der Nerventätigkeit, Arch. f. d. ges. Physiol. **226**:600-658, 1931.

of the mechanisms of spatial orientation and regulation of intensities of reaction suggests that the nervous organizations involved must be different and incapable of unrestricted function within the same anatomic field. The available facts of localization seem consistent with such an assumption. Studies of the visual system have shown a dissociation of functions which seems inexplicable on any other basis. In the rat destruction of the striate areas permanently abolishes detail vision, leaving unimpaired the ability to discriminate differences in the intensity of light. Injury to the superior colliculi alone produces some impairment of brightness vision, without destroying the capacity for detail vision. Destruction of the striate areas, with serious injury to the colliculi and optic thalamus, precludes the formation of any habits based on vision. In animals without the visual cortex reaction is determined by the total amount of light entering the eye: Difference in the area of luminous surface is equivalent for behavior to difference in surface luminosity.[3b]

The condition is probably similar in higher mammals. Marquis[14] showed the persistence of brightness vision in the dog after destruction of the visual cortex, and Klüver[15] found normal sensitivity to light in lower monkeys from which the whole of both occipital lobes was removed.

The visual cortex, functioning in the differentiation of small spatial differences of retinal excitation, shows a high degree of internal anatomic and functional differentiation. The available evidence indicates little or no subordinate functional localization within the colliculus, although the quadrants of the retina have separate projections on its surface.

Thus, in spite of the fact that brightness seems psychologically a characteristic of visual form, the two variables position and intensity seem to be integrated at different levels of the nervous system, with no evidence yet as to where the final integration takes place which gives them psychologic unity.

In contrast to the visual cortex, most intimately concerned in the space system, are the olfactory centers and the olfactory cortex. Olfactory experience is lacking in spatial character. In spite of the numerous centers and elaborate structure of the olfactory system, clinical studies and the experimental investigations of Swann[16] have failed to reveal

14. Marquis, D. G.: Effect of Removal of the Visual Cortex in Mammals, with Observations on the Retention of Light Discrimination in Dogs, A. Research Nerv. & Ment. Dis., Proc. **13**:558-592, 1934.

15. Klüver, H.: An Analysis of the Effects of the Removal of the Occipital Lobes in Monkeys, J. Psychol. **2**:49-61, 1935.

16. Swann, H. G.: The Functions of the Brain in Olfaction: II. The Results of Destruction of Olfactory and Other Nervous Structures upon the Discrimination of Odors, J. Comp. Neurol. **59**:175-201, 1934.

any subordinate localization. Herrick [17] pointed out that the structure of the olfactory bulb and the lower centers is especially adapted to facilitative effects, and the recent studies of Lorente de Nó [18] showed a mechanism for recurrent excitation in the cornu ammonis which seems especially adapted for summation. The absence of subordinate localization in a system adapted to facilitative effects is consistent with my hypothesis.

In motor functions the picture is similar. There are indications that many isolated masses of cells in the central nervous system are concerned with regulation of the general level of excitation and that they contribute little, if anything, to the specific patterning of reaction. The cerebellar system, the corpus striatum and basal cerebral nuclei and, in general, the structures making up Hunt's paleokinetic system [19] seem to be of this character.

Lesions in such systems result in global symptoms of decreased force and steadiness or inaccurate timing of movements, without marked change in the combination of muscles employed in voluntary acts. Within such centers there is generally little evidence of subordinate specialization, either structural or functional.

The motor cortex represents the opposite extreme—an area with highly specialized internal arrangement. For this area there is little evidence of gradation of response with intensity of excitation. With electrical stimulation the responses are generally of an all or nothing character, and an increase in the intensity of stimulation produces longer after-discharge, rhythmic oscillation of movement or irradiation to other muscle groups rather than simple increase in the intensity of reaction.

Thus, in both sensory and motor systems there are indications of the separation of mechanisms having to do with reactions to space and to intensity. This is consistent with my assumption that these functions involve different and incompatible kinds of nervous organization and that the reason for separate localization of the functions is that the same group of nerve cells cannot give graded responses by irradiation and also preserve the spatial relations of sensory excitation. This hypothesis cannot be applied too rigidly. It is possible that such a field as the motor cortex may consist of an aggregation of cell groups, each behaving as an excitable unit in space reactions while organized to give graded responses by irradiation restricted within the individual unit.

---

17. Herrick, C. J.: An Introduction to Neurology, ed. 5, Philadelphia, W. B. Saunders Company, 1931, p. 261.

18. Lorente de Nó, R.: Studies on the Structure of the Cerebral Cortex: II. Continuation of the Study of the Ammonic System, J. f. Psychol. u. Neurol. **46**:113-177, 1934.

19. Hunt, J. R.: The Static and Kinetic Systems of Motility, Arch. Neurol. & Psychiat. **4**:353-369 (Oct.) 1920.

Likewise, the small amount of detail vision shown by animals lacking the striate areas implies that within the subcortical visual centers which are primarily concerned with intensity of the stimulus there is some focalizing and limited irradiation of excitation.

The evidence for the separation of these two functions is not conclusive, since too little is known of any area to delimit its functions clearly, but the hypothesis suggested makes intelligible some of the facts of localization which are otherwise wholly mysterious.

Orientation in space and regulation of intensity are only two of several or many integrative processes which contribute to the total picture of behavior. If my hypothesis is correct, that separate localization is determined by incompatibility of nervous mechanisms, there should be other fundamental nervous organizations or processes which cannot be combined with these two and which will account for still different types of localized function. One such organization is suggested by the problem of serial order in behavior.

Serial Order in Reactions.—The least studied and most obscure problems of nervous organization are presented by the temporal aspects of behavior. Every action above the level of a spinal reflex involves time factors for which there is available no adequate explanation. Control of speed and duration enters into the simplest adaptive movement. Accurate timing of the separate components of an organized movement is as important as the spatial pattern. Most adaptive activities depend on the serial release of a succession of movements in a predetermined order, as in the production of a musical phrase or a grammatical form in speech.

Understanding of these problems has been delayed and confused by the doctrine of chain reflexes, which attempts to account for each act of the series as a reaction to sensory excitations from the preceding act. This doctrine is utterly without foundation. I have shown that the control of speed and accuracy of movement may be unimpaired in a limb totally insensitive to movement.[20] The interval between successive movements of a musician in playing rapid scale passages is less than the reaction time to kinesthetic stimulation. Ball and I[21] showed that the serial activities of the animal in maze running may be independent of sensory cues. A large amount of evidence, such as transposition of a musical phrase to any key or the grammatical use of newly acquired words, makes it clear that the order of the series of acts is relatively independent of the particular form of the acts which con-

20. Lashley, K. S.: The Accuracy of Movement in the Absence of Excitation from the Moving Organ, Am. J. Physiol. **43**:169-194, 1917.

21. Lashley, K. S., and Ball, J.: Spinal Conduction and Kinesthetic Sensitivity in the Maze Habit, J. Comp. Psychol. **9**:71-105, 1929.

stitute it and therefore cannot be interpreted as a chain of habits. The doctrine of chain reflexes must be abandoned, and some other explanation of serial acts must be sought.

A clue to the possible mechanism is given by the studies of limb coordination reported by Buddenbrock [22] and Bethe.[23] Coordinated movements following the amputation of one or more legs in arthropods and vertebrates were observed, and immediate reorganization adapted to progression was found to occur spontaneously, often with complete reversal of the normal reciprocal relations of the movement of different legs. Without consideration of details, the mechanism of coordination suggested by these studies is somewhat as follows: In the ganglionic chain only limb centers participate in coordination which are in a state of tonic excitation from sensory stimulation of the limb. Dominance or lead in progression is taken by the most anterior functioning center on each side, which may be interpreted in terms of Child's conception of polarization of neuron systems.[24] Reciprocal relations of the centers are determined by their relative ipsilateral and contralateral positions with respect to the dominant centers.

Details of the mechanism are, of course, obscure, but it seems probable that in this system spatial position of the center with reference to polarity of the system as a whole and to the excitation of other centers is the determining factor for the serial order of movement. Turning to activities of higher levels, one finds reasons for believing that temporal relations are determined by spatial patterns of excitation. Koffka [25] reached this conclusion from psychologic considerations. His fundamental argument was that the memory trace of a stimulus and the process by which it is identified with a current repetition of the stimulus cannot be identical and therefore cannot be localized in the same neurons—that the temporal aspects of experience must therefore have a spatial basis.

There are indications that the production of an ordered series of acts involves preliminary simultaneous priming or subliminal excitation of many or all of the acts, with subsequent supraliminal excitation in predetermined order. Evidence for this comes from contaminations in speech and other serial acts—anticipations of words which should

22. Buddenbrock, W.: Der Rhythmus der Schreitbewegung der Stabheuschreche Dyxippus, Biol. Zentralbl. **41**:41-48, 1921.

23. Bethe, A.: Plastizität und Zentrenlehre, in Bethe, A.; von Bergmann, G.; Embden, G., and Ellinger, A.: Handbuch der normalen und pathologischen Physiologie, Berlin, Julius Springer, 1931, vol. 15, p. 1175.

24. Lillie, R. S.: Protoplasmic Action and Nervous Action, Chicago, University of Chicago Press, 1923, pp. xii and 417.

25. Koffka, K.: Principles of Gestalt Psychology, New York, Harcourt, Brace and Company, Inc., 1935, p. 438.

come later, as in spoonerisms, confusions of alternative words and the like. This also implies a spatial representation of the temporal series.

Such considerations are not conclusive; yet the best guess that can be made from psychologic evidence is that temporal phenomena in behavior are dependent on spatial relations in the nervous system. Is there evidence for separate localization of the mechanisms for serial timing? Clinical symptoms suggest it. In apraxia, in syntactic (transcortical, agrammatical) aphasia and in some cases of sensory aphasia the primary defect seems to be in the temporal ordering of activity. Confusions and contaminations of act or speech become more frequent; the execution of an ordered series of acts becomes impossible, although the isolated acts may still be performed. Recent experimental work on the functions of the frontal lobes suggests that one of the major functions of this region may be the elaboration of such temporal schemata.

If temporal order is determined by space factors in the nervous system, the fields in which this type of organization is dominant cannot also serve in other space systems. There is thus some reason to believe that the utilization of the spatial arrangement of excitations in the timing functions determines an additional group of isolated cerebral areas.

HIGHER ORDERS OF INTEGRATION

The physiologic basis of the more complicated modes of behavior is still a mystery, but it seems probable that the same separate localization of "patterning" and of dynamic processes holds for them as for the simpler sensory and motor activities. Many students of clinical neurology have felt the need for a general conception to cover observed variations in the level of efficiency, such as are described by Head's conception of "vigilance" [26] and which affect the readiness of elicitation of response rather than its form.

There are many indications that the general level of excitability of a center depends on facilitative effects from various sources. Thus, the early work of Munk showed that the deafferented paw of a dog is not ordinarily used to hold a bone in feeding, though it can be so used when the intact paw is restrained. The same condition is apparent in cerebral paralysis in the monkey, when intense excitement will lead to temporary use of the paralyzed limbs.[27] In such cases the organized

26. Head, H.: The Conception of Nervous and Mental Energy, Brit. J. Psychol. (Sect. Gen.) **12**:126-147, 1923-1924.

27. Munk, H.: Ueber die Folgen des Sensibilitätsverlustes der Extremität für deren Motilität, Sitzungsb. d. k. Akad. d. Wissensch. math.-naturw. Cl., 1903, pp. 1038-1077. Lashley, K. S.: Studies of Cerebral Function in Learning: V. Retention of Motor Habits After Destruction of the So-Called Motor Areas in Primates, Arch. Neurol. & Psychiat. **12**:249-276 (Sept.) 1924.

pattern of the movements has not been destroyed, but the excitability of the final common path is greatly reduced, apparently as an affect of diaschisis, since emotional facilitation can still elicit the reaction. Such dynamic deficiencies are apparently responsible for many disturbances of more complex behavior.

Amnesia.—In the course of normal forgetting the possibility of recall may be lost; yet traces of the former memory can be demonstrated by the "savings method" of relearning. The amount of practice necessary for relearning is a function of the time elapsed since the original learning. The memory trace may thus exist at different levels of availability for recall, which in physiologic terms are probably represented by levels of excitability. In experiments on postoperative amnesias I found that the amount of practice necessary to reestablish a habit is proportional to the extent of the lesion,[28] and Hu [29] showed that the rate of forgetting of habits formed after cerebral operation is also a function of the lesion. These experimental results suggest that the organic amnesia is a weakening of the memory trace, of the same nature as that which normally results from lapse of time.

In mild amnesic aphasia and other organic disorders of memory in man, the condition may be described as difficulty of recall rather than absolute destruction of traces. Recall may be effected by associative aids when spontaneous recall does not occur,[30] and affectively toned words are most likely to be preserved (emotional facilitation). Such facts suggest that the pattern of the trace is not destroyed in pure organic amnesia and that the defect is rather a reduction of excitability. The fluctuations in severity of symptoms reported by Franz [31] bear this out.

Agnosia.—In contrast to the amnesias, there is another general type of disorder in which the major symptom is disorganization of the integrated patterns. Klüver [32] found that after various cerebral lesions in macaques, the ability to make comparisons of sensory stimuli was lost for a considerable period. Once the trick of comparing was again

---

28. Lashley, K. S.: Mass Action in Cerebral Function, Science **73**:245-254 (March) 1931. Lashley, K. S., and Wiley, L. E.: Studies of Cerebral Function in Learning: IX. Mass Action in Relation to the Number of Elements in the Problem to Be Learned, J. Comp. Neurol. **57**:3-55, 1933.

29. Hu, Chi-Nan: The Effects of Brain Injury upon Retentiveness in the Rat, University of Chicago, 1934, unpublished dissertation.

30. Head, H.: Aphasia and Kindred Disorders of Speech, London, The Macmillan Company, 1926.

31. Franz, S. I.: On Certain Fluctuations in Cerebral Function in Aphasics, J. Exper. Psychol. **1**:355-364, 1916.

32. Klüver, H.: Personal communication to the author.

acquired, all the habits based on sensory discrimination, tactile, visual and kinesthetic, immediately reappeared. The defect in these cases was distinctly different from the usual amnesia. It involved a disturbance in the mode of integrating or organizing excitations without reduction in the availability of the associated reactions when this type of organization was again reestablished. Many of the symptoms of apraxia, visual agnosia, agrammatism and semantic aphasia seem to be of this character. Certain modes of relating experience are disturbed, without fundamental amnesia. The disorder may occur at a perceptual level, as in the loss of spatial attributes in the visual field, or at various higher integrative levels.

In amnesia and agnosia there is thus the same contrast of dynamic and patterning mechanisms which appeared in the separation of fields concerned with space and with intensity. There are only vague indications of the interplay of these mechanisms. I have shown that in the rat habits based on the recognition of visual objects are not disturbed by any cerebral lesion which leaves intact any small part of the binocular projection field of the striate area. This indicates that the efficiency of a mechanism concerned in patterning behavior is not greatly reduced by extensive injury and that therefore the dynamic aspects of amnesia are probably not the result of direct injury to the patterning mechanism.

In these experiments on visual memory the lesions were not large enough to produce serious general deterioration. From other sources there is evidence that larger lesions in any part of the cortex produce general lowering of efficiency. Tsang [33] showed that in rats blinded at birth lesions limited to the area striata produce severe retardation in maze learning and, hence, that the primary visual cortex has an important nonvisual function. I have shown that the retarding effects of lesions of equal area in different parts of the cortex are practically identical in a variety of types of learning. I have interpreted such results as evidence that, in addition to their specific functions, all parts of the cortex exercise a general facilitative effect on the rest. It is possible that in higher animals cortical areas having more localized facilitative functions may have developed and that some of the specific dynamic disturbances observed clinically may be due to their injury. Whether this is the case or whether the observed dynamic disturbances are really the expression of general lowering of functional efficiency can be determined only by more detailed studies of the range of defect in various types of disorder.

33. Tsang, Yü-Chüan: The Functions of the Visual Areas of the Cerebral Cortex of the Rat in the Learning and Retention of the Maze, Comparative Psychology Monograph, serial no. 50, Baltimore, Johns Hopkins Press, 1934, vol. 10, pt. 1, pp. 1-56; ibid., serial no. 57, 1936, vol. 12, pp. 1-41.

PHYSIOLOGIC INTERPRETATION OF LOCALIZATION

Nearly a century of psychologizing concerning the cerebral cortex has added practically nothing to knowledge of its fundamental activities. The transmission, summation and inhibition of nerve impulses, with such obscure processes as are implied in humoral and electronic conduction, form the real basis of nervous integration and the foundation on which understanding of cerebral function and of the problems of behavior must be built. So far as it is not an accident of development, the separation of functions shown in cerebral localization must be due to some physiologic necessity. The phenomena of behavior and of "mind" present problems to the neurophysiologist and define the physiologic mechanisms in terms of what they can accomplish but give no clue to the nature of the integrative processes.

Knowledge of such processes in the cortex is still too limited to permit of anything but vague speculations concerning their nature, largely inferred from the phenomena of behavior. The direction of the speculations, however, is important for the development of further research. It has been assumed that the properties of experience are represented at the level of some simple nervous activity or in single loci: sensations in the sensory areas, volitional patterns in the motor regions or particular forms of intelligent behavior in restricted coordinating centers. Such conceptions of localization are oversimplified and must be abandoned. Nothing is known of the physiologic basis of conscious states, but there is some reason to believe that these states can be correlated only with the summated activity of all centers simultaneously excited. The position of Goldstein, that the functions of every center are dependent on its relations to the rest of the intact nervous system,[34] cannot be too strongly emphasized in considering problems of neuropsychology. Conceptions of the organization of mind or of behavior are based on a logical analysis of the activities of the total organism, and the final synthesis of nervous states which constitute these activities must transcend the excitation of any single center.

Thus, one must expect to find fractionings of behavior following organic lesions which cannot be expressed or understood in the current psychologic terminology. Indeed, psychologists are in scarcely better case than neurologists when it comes to interpreting the fundamental variables of behavior. The recently developed technics of factor analysis often reveal variables which are difficult to identify with any psychologic units. The "unit traits" or mathematical abstractions which account for correlations of ability in different tasks often indicate relations which are as unintelligible in terms of the total behavior pattern as are the

34. Goldstein, K.: Der Aufbau des Organismus, The Hague, Netherlands, M. Nijhoff, 1934.

symptoms of organic lesion of the brain. The technic of factor analysis has been criticized for this failure to reveal expected relationships; yet this very fact may be an argument in its favor. A single physiologic variable may well contribute to activities which are logically unrelated, and the most bizarre results of factor analysis may become quite reasonable when the physiologic variables are understood. The functional units of behavior must be determined by the exigencies of nerve conduction and integration.

The problem of why there is localized specialization of function in the nervous system is far from solved by the hypotheses which I have formulated in this paper. But the hypotheses may serve to point the contrast between the physiologic point of view and the mixed metaphysics of the current mentalistic interpretations of localization. Not the logical sequences of a course in Euclid but the interplay of nerve impulses determines the localization of intellect and the variables which enter into it. There is small chance of understanding either the phenomena of localization or the physiologic basis of logic until they can be cast in terms of elementary nervous activities.

SUMMARY

In the foregoing discussion I have sought to illustrate a physiologic approach to the problem of cerebral localization. Various lines of evidence indicate that the spatial distribution of excitations within a nerve center may form the basis for several types of integration, such as the regulation of intensity of discharge, the establishment of fields of force to determine spatial orientation and the control of the serial timing of activities. Each of these functions implies a different mechanism of organization and, consequently, a spatial separation of the fields in which the different processes operate. Experimental and clinical data indicate that the dissociation of functions resulting from cerebral lesions is in harmony with the assumption that cerebral localization is determined by the separation of such incompatible mechanisms.

Obituaries

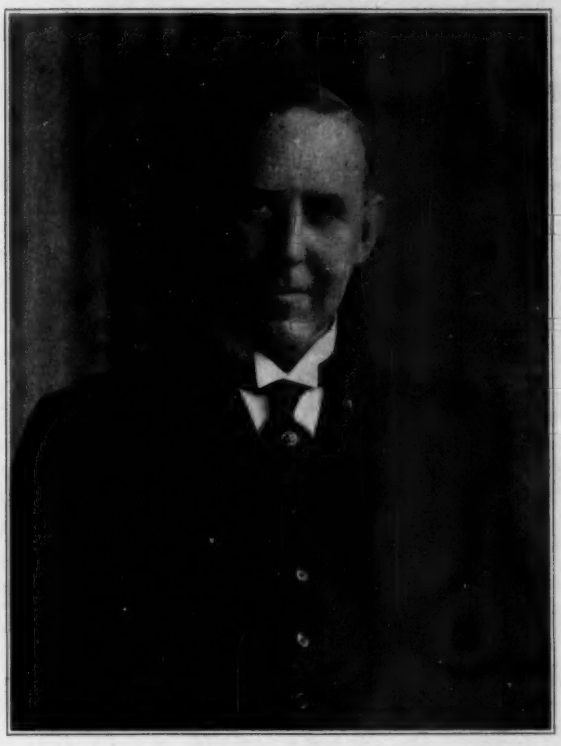
SAMUEL ALEXANDER KINNIER WILSON, M.D., D.Sc., F.R.C.P.*

Physician to the National Hospital, Queen Square, London, and to the King's College Hospital; Honorary Member of the American Neurological Association

It is not an easy thing to write here of Kinnier Wilson, who has so lately left our company. His was a character and personality perhaps a little unlike the times—an *originale,* as indeed I think he would have been amused to be considered. His thinking was far from the conventional pattern—with a mind rich and flexible, pellucidly clear and powerful enough to pierce the many veils that lay between him and the truth he sought. An untiring worker, a stylist but no pedant, his iridescent humor played puckishly over all his intellectual activities, and in the midst of his deepest absorption in a problem he would stop to joke and laugh at his own gravity. In our younger days there was to us always something olympian in Wilson's manner—we, his juniors, always called him "God!"—his tolerant condescension toward our errors gave us as much joy and merriment as it certainly gave him. Perhaps, however, he was too consciously aware of himself to be entirely happy—his happiness came from his flashing sense of values and the incongruity of events and circumstances; a sardonic courage and an ironical humor were the defenses of a nature too sensitive for inner gaiety. He suffered fools far from gladly and withered them with a word—and they, less quick of thought, were then often bewildered and sometimes resentful. He was impatient of stupidity but utterly gentle and kind to intellect and effort. His letters were a titillating joy—rich in allusion and funny references. They were the expression perhaps of the best of him; one, written just before his death, when he knew he would not write another, ended with affectionate wishes for me "in that marvelous city of yours, full of polyglotted peoples." Few in the medical profession have had so splendid an acknowledgment of merit from foreign nations—Japan, Italy, Poland, Germany, Austria, Denmark and the United States all delighted to adopt him as an honored name in their intellectual societies. Indeed, all his contributions to learning in Britain and abroad had something in them of the grand manner and a distinction of style for which he labored so successfully that its appearance to the untutored seemed, erroneously, a happy and facile gift. Perhaps his most important single contribution was in 1911, now known simply by his name, whereby he, for the first time, pushed

* Dr. Wilson died in London, May 12, 1937.

open the door of knowledge of the use and function of the lenticular nuclei. Here was the first proof of the relationship between abnormal dystonic movements and abnormal tone and the structure of the putamen and caudate nucleus. His gift for dramatic exposition and his commanding presence made him a great teacher, while the simple phrasing and logical sequence of his thought made complex subjects, like aphasia and the epilepsies, fascinating and almost oversimplified delights—and not the least of these delights might be his parenthetical scorn of the



SAMUEL ALEXANDER KINNIER WILSON

jargon-mongers and their neologisms. He went out when his light was brightest, when his powers were fullest—when he would have given us more knowledge and reaped, too, the rewards of large attainment. Sponsored by Sherrington and Adrian for the fellowship of the Royal Society, he died before his election; the "Textbook of Neurology," which was to be his great achievement, was still unfinished; this is vast loss to us, for Kinnier Wilson had the intellect, the artistry and the philosophy by which to give us the book of leadership. He wore the mantle of the masters; and one feels deeply the true measure of a man when he has gone away.

FOSTER KENNEDY, M.D.

Abstracts from Current Literature

Anatomy and Embryology

CORTICIFUGAL FIBER CONNECTIONS OF THE CORTEX OF MACACA MULATTA: THE OCCIPITAL REGION. FRED A. METTLER, J. Comp. Neurol. **61**:221 (April) 1935.

This is one of a series of studies of the cortical connections in Macaca mulatta. Lesions were produced in four cortical regions, and the brains were subsequently stained by the Marchi method. In some cases the thalamus was studied by the Weigert, silver and Nissl methods. From four to seven animals were used in each group.

When the lesion was in the occipital region, association fibers from the upper portion of the opercular striate cortex were seen to pass mainly to the other parts of the striate cortex, to the lower macular cortex and to the posterior limb of the angular gyrus. Areas which differed in major cyto-architectural details were reported to have different associational connections. At least one component of the cingulum seemed to be composed of fibers of intermediate length originating in the region of the calcarine fissure and passing not farther forward than the paracentral lobule. The tapetum seemed to consist partially of incoming callosal fibers, passing through which were fibers of the optic radiation and short association fibers. In the radiation of Gratiolet were seen outgoing callosal, occipitothalamic and mesencephalic fibers, and passing through it were likewise incoming callosal fibers and short association fibers. No corticopontile or corticomesencephalic fibers were traced from the macular area.

FRASER, Philadelphia.

CORTICIFUGAL FIBER CONNECTIONS OF THE CORTEX OF MACACA MULATTA: THE FRONTAL REGION. FRED A. METTLER, J. Comp. Neurol. **61**:509 (June) 1935.

Five animals were subjected to different lesions of the frontal cortex. A lesion of the precentral gyrus (except the eyelid area of Horsley) revealed short association fibers passing anteriorly to the rest of areas 4 and 6 and long association fibers passing as far as the occipital pole. Degenerated fibers were also seen in the septum pellucidum. Widespread degeneration showed in the lateral thalamic nucleus. Some degenerated fibers followed the medial lemniscus into the midbrain. Large degenerated fibers passed to the red nucleus and the posterior commissure. No corticopontile degeneration was observed. Degenerated fibers were seen in the decussation of the brachium conjunctivum and were distributed to various cranial motor nuclei. Mettler does not mention these as evidence of an aberrant pyramidal tract.

In another experiment the ventral half of the superior frontal gyrus, the entire middle frontal gyrus and the dorsal half of the inferior frontal gyrus were destroyed. Association fibers were seen going to all parts of the cortex. Fine fibers entered the caudate nucleus and putamen and formed Muratoff's subcallosal bundle. The globus pallidus, the anterior portion of the lateral thalamic nucleus, the substantia nigra and the anterior part of the red nucleus showed degenerated fibers. Most of the degeneration in the substantia nigra was in the pars reticularis. Corticopontile degeneration was seen.

In the next experiment Mettler made a very small surface lesion which destroyed the cortex at the foot of the inferior precentral sulcus and the subcortex in an area extending backward and medially beneath the insula to the region of the putamen in such a way as to avoid degeneration in the internal capsule. Many association fibers were demonstrated. The globus pallidus was the only nucleus to show degenerated fibers.

In another experiment two small independent and completely separate lesions were produced, one of which lay in the middle of the anterior central gyrus

and the other within the angle of the inferior precentral sulcus and its horizontal limb. Short association fibers passed to all other gyri in the region except the orbital. No projection fibers from the anterior lesion were seen, but from the posterior lesion fibers proceeded to the gray matter around the aqueduct and to the lateral thalamic nucleus and the pulvinar.

FRASER, Philadelphia.

CORTICIFUGAL FIBER CONNECTIONS OF THE CORTEX OF MACACA MULATTA: THE PARIETAL REGION. FRED A. METTLER, J. Comp. Neurol. **62**:263 (Oct.) 1935.

The brains of seven animals were studied after surgical lesions of the parietal cortex. Mettler found that Brodmann's cortical area 18 was especially related to the visual region. Lesions in the central parietal cortex showed poor connections with the motor area, but lesions in the parareceptive cortex revealed important connections with the motor region. As in all regions studied, the fibers which crossed to the opposite side observed the principle of heterolateral cortical callosal association. Many projection fibers were seen passing into the dorsal half of both segments of the globus pallidus. All the parietal areas except the angular gyrus were seen to project on the lateral thalamic nuclei. The angular gyrus projected especially on the pulvinar. The substantia nigra received fibers from the parietal region. The ocular nuclei (interstitial, oculomotor, trochlear and abducens) and the central gray matter also received fibers from this region. The trigeminal complex, the facial nuclei and the inferior olive received fibers from the anterior end of the intraparietal sulcus. Corticosubthalamic fibers arose from the anterior and posterior marginal gyri, as well as from the anterior end of the occipitotemporal gyrus and the upper ends of the superior and middle temporal gyri. Fibers to the lateral geniculate body arose in the angular, occipitoparietal and occipitotemporal gyri.

FRASER, Philadelphia.

CORTICIFUGAL FIBER CONNECTIONS OF THE CORTEX OF MACACA MULATTA: THE TEMPORAL REGION. FRED A. METTLER, J. Comp. Neurol. **63**:25 (Dec.) 1935.

The evidence presented here is based on experimental material comprised of the brains of four animals subjected to surgical lesion of the temporal region.

Short association tracts were seen passing to the superior frontal, the anterior central and the postcentral gyrus and others to the temporal gyrus, the hippocampal gyrus, the gyrus cinguli and the insula. Heterolateral cortical callosal association fibers were always seen. When the lesion was only cortical, no projection fibers were described from the temporal area. If the underlying white substance was cut, projection fibers were reported passing to the globus pallidus and the medial nucleus of the thalamus, the corpus subthalamicum, the red nucleus, the interstitial nucleus, the pulvinar and the substantia nigra. The superior temporal gyrus sent fibers to the medial geniculate body. The middle temporal gyrus sent fibers to the pons.

FRASER, Philadelphia.

OPTIC CONNECTIONS OF THE DIENCEPHALON AND MIDBRAIN OF THE CAT. R. W. BARRIS, W. R. INGRAM and S. W. RANSON, J. Comp. Neurol. **62**:117 (Aug.) 1935.

For the study of the optic connections of the diencephalon and midbrain, twenty-six cats were subjected to operative procedures. In the first series one or two eyes were removed from the animal. The Marchi technic was applied after from nine to eleven days, as had been allowed for degeneration. In another series both eyes were removed, and from six to eight months was allowed for complete degeneration. Then each animal was given a small lesion in the dorsal nucleus of the lateral geniculate body, with the aid of the Horsley-Clarke stereotaxic instrument. From nine to eleven more days was allowed for this degeneration, and the Marchi technic was applied. In the third series a portion of the

right visual or striate area was removed. From nine to eleven days was allowed to elapse, and the Marchi technic was applied. In the fourth series a part of the right parastriate area was removed, and the animals were treated as were the cats in the third series.

In the cat most of the optic nerve fibers are crossed. The authors conclude that one and the same fiber of retinal origin may mediate visual impulses to the dorsal nucleus of the lateral geniculate body and, at the same time, may pass onward to participate in the various reflex activities of the tectum of the midbrain. Few, if any, fibers showed synaptic connections in the ventral nucleus of the lateral geniculate body, but fibers pass through it on their way to the dorsal nucleus. The retinal fibers establishing connections with the superior colliculus occupy the more dorsal part of the stratum opticum. In cats, after removal of one or both eyes, degeneration was seen along the stratum zonale of the caudal part of the thalamus. After degeneration from lesions of the dorsal nucleus of the lateral geniculate body, fibers were seen only in the optic radiation, and these reached the cortex. Fibers leaving both the striate and the parastriate areas of the cortex go to the superior colliculus, the stratum opticum, the nucleus of the optic tract and the pontile nuclei. The pulvinar does not seem to be an end-station for fibers either from the retina or from the striate or parastriate cortex.

FRASER, Philadelphia.

THE EXTENT AND STRUCTURE OF THE ELECTRICALLY EXCITABLE CEREBRAL CORTEX IN THE FRONTAL LOBE OF THE DOG. WILBUR K. SMITH, J. Comp. Neurol. **62**:421 (Oct.) 1935.

This study was made to determine the relation between the electrically excitable cortex and the cyto-architectural structure. Electrical stimulation was carried out with an alternating current on the exposed brain of anesthetized dogs. Tracings of each brain were made to show the blood vessels. The extent of the excitable cortex was plotted on the tracing. The brain was then fixed in situ. Blocks of cortex were removed and embedded and the sections stained with thionine.

Electrical stimulation of the cortex of the lateral part of the anterior sigmoid gyrus always resulted in contractions of voluntary striated muscle, with visible muscular movement. This cortex belongs to the precentral gigantopyramidal type (are 4 of Brodmann). No contraction was observed on stimulation of its medial portion, where the cortex belongs to the agranular frontal type (area 6 of Brodmann). The electrically excitable area in the posterior sigmoid gyrus was found to extend the entire length of the gyrus but to include only its rostral portion. The cortex here belongs to the precentral gigantopyramidal type. The rostral part of the coronal gyrus was also excitable, but although this area belongs to area 4, the pyramidal cells of the fifth layer are not of the giant cell type.

ADDISON, Philadelphia.

POSTERIOR COLUMN FIBERS AND THEIR TERMINATION IN MACACUS RHESUS. A. FERRARO and S. E. BARRERA, J. Comp. Neurol. **62**:507 (Oct.) 1935.

The purpose of the investigation was to establish for clinical purposes how much of the symptoms due to damage of the posterior columns, particularly in the upper segments of the cord, is cerebellar in nature, due to the connections of the fibers of the posterior column with the external cuneate nucleus and ultimately with the cerebellum.

Ten protocols are presented to demonstrate experimentally that the fibers of the funiculus cuneatus end not only in the nucleus cuneatus but in the external cuneate nucleus, or the nucleus corporis restiformis or the Clarke-Monakow nucleus, as it is called by Ferraro and Barrera. The origin of the fibers ending in the Clarke-Monakow nucleus is in all the cervical roots and the four highest thoracic roots. No fibers from the seventh thoracic root or below were

seen to enter this nucleus. The fibers from the upper cervical roots terminate in the most ventrolateral part of the nucleus and those from the lower cervical and higher thoracic roots terminate in the mediodorsal portion of the nucleus, thus producing a lamination. Lamination was also seen in the nucleus gracilis in two dimensions, mediolateral and caudocephalic. FRASER, Philadelphia.

THE CYTOLOGICAL CHANGES IN THE HYPOPHYSIS CEREBRI OF THE GARTER SNAKE (THAMNOPHIS RADIX) FOLLOWING THYROIDECTOMY. KENNETH A. SILER, J. Morphol. **59**:603 (Sept.) 1936.

The hypophysis cerebri of the garter snake, Thamnophis radix, does not differ greatly in its gross or microscopic structure from that of other vertebrates. It consists of an infundibular stalk, the pars nervosa, the pars intermedia and the pars anterior and lies in a bony sella turcica. A connection between the anterior part of the pars anterior and the infundibular stalk—the pars terminalis—is present. In the pars anterior alpha and beta cells and nongranular chromophobe cells are observed, although the chromophobe cells are scarce.

After thyroidectomy the chromophobe cells enlarge, acquire a basophilic granulation and become apparently normal beta cells. Then these, along with the beta cells originally present, become vacuolated, lose their granules and finally degenerate. The number of alpha cells is also reduced. In animals kept at 90 F. after thyroidectomy, the degeneration of beta cells is less than that in animals kept at 70 F. It is suggested, however, that the alterations described in the anterior lobe of the pituitary are not due solely to metabolic upset. WYMAN, Boston.

THE SUBTHALAMUS AND STRUCTURES OF THE SUBTHALAMOMESENCEPHALIC REGION. G. ROUSSY and M. MOSINGER, Rev. neurol. **64**:637 (Nov.) 1935.

The authors have continued their anatomic study of this difficult region of the base of the brain and have come to the following conclusions: The subthalamus is composed of a number of distinct nuclear formations, six of which are chosen for special study: the nucleus reticularis internus, the nucleus of the zona incerta, the nucleus of field H_1, the nucleus of field H_2, the nucleus reticularis externus and the corpus subthalamicum. There are many association fibers among the various nuclei. Most of the afferent fibers come from the striatum, the pallidum and the nucleus entopeduncularis, so that an extrapyramidal function can be assigned to the various nuclei mentioned. On the other hand, there is a poverty of fibers coming from the cortex. The relationship between the subthalamus and the nucleus reticularis of the thalamus, which has cortical connections running in both directions, is probably the main connection between the cortex and the hypothalamus. Afferent fibers of the olfactory type also reach the subthalamus, and obviously many visual connections are present. A few sensory fibers reach the nucleus reticularis by the mamillary peduncle, but most of them come directly from the thalamus, probably by way of the H_1 field. A few of the dentatorubral fibers reach this vicinity, and there are certain connections with the medial longitudinal fasciculus. The subthalamus thus receives extremely varied afferent fibers, and, in addition, it has many connections with the vegetative hypothalamus. These last connections explain in large part the association of vegetative and motor reactions. FREEMAN, Washington, D. C.

PHYSIOLOGIC FUNCTION OF THE ORBICULARIS PALPEBRARUM MUSCLE AND THE PROBLEM OF THE SUPERIOR PORTION OF THE FACIAL NERVE. E. VELTER, Rev. d'oto-neuro-opht. **13**:435 (June) 1935.

The muscles actuating the eyelid may act singly, but more often they participate in associated complex movements that protect the eye, result in winking and assist in movements of mimicry. Global paralysis of the orbicularis muscle produces lagophthalmos, epiphora and eversion of the punctum. Excitation *en masse* causes

blepharospasm; certain localized spasms produce spasmodic entropion or ectropion. The orbicularis muscle is innervated by branches of the superior portion of the facial nerve. While it has generally been supposed that only the inferior branch of the facial nerve is involved in facial paralysis accompanying hemiplegia, Dejerine maintained that the superior branch is always involved as well, but to a far less noticeable degree. Physiologic and clinical data show the relative independence of the superior branch of the facial nerve. After discussion of the observations and researches of a number of investigators. Velter concludes that there is no evidence that proves the existence of a separate nucleus in the midbrain or in the cortex for the superior branch of the facial nerve. Autonomy of this branch depends on bilateral corticonuclear connections through a double pathway: the geniculate bundle, on the one hand, and the pathway of aberrant fibers, on the other. There is still much that is not known about the complex nervous mechanism involved in winking. The ophthalmic and optic nerves compose the centripetal leg of the reflex arc. The fibers in the fifth nerve enter the descending root and arrive at the gelatinous substance of Rolando. The centrifugal pathway is formed by the common motor oculi nerve (third nerve) and the facial nerve. A bilateral central innervation is necessary to explain the normal bilaterality of winking and its persistence in cases of isolated paralysis of the third and the seventh nerves.

DENNIS, San Diego, Calif.

Physiology and Biochemistry

THE EFFECT OF INJECTING CERTAIN ELECTROLYTES INTO THE CISTERNA MAGNA ON THE BLOOD PRESSURE. HARRY RESNIK, M. F. MASON, R. T. TERRY, COBB PILCHER and T. R. HARRISON, Am. J. M. Sc. **191**:835 (June) 1936.

When solutions of potassium chloride ranging from 50 to 100 millimols per liter were injected intracisternally in dogs in doses of 1 cc., a marked rise in the blood pressure occurred. Respiration was usually increased, and restlessness, rigidity, opisthotonos and muscular twitchings were frequent. Special experiments seemed to show that the site of action of the injected solution was between the inferior colliculus and the outlet of the fourth ventricle. Although the chloride, lactate and gluconate salts of calcium had slight effect on the blood pressure, they had a striking inhibitory action on the pressor effect of potassium chloride injected subsequently. The lack of correlation between the height of the calcium content of the spinal fluid and the effectiveness of the calcium salt in preventing the rise of blood pressure produced by injections of potassium chloride was apparent, suggesting that the calcium content of the nerve tissue itself is the important consideration. After the injection of 1 cc. of the chloride, sulfate or nitrate salt of sodium in concentrations up to 200 millimols per liter, salts such as sodium oxalate, sodium phosphate and sodium citrate, which diminish the ionization of calcium, had marked pressor effects. Salts of magnesium have a similar, but less pronounced, effect than calcium salts. Lead caused a delayed, but prolonged, rise in blood pressure. Only the ionized calcium is of importance in inhibiting the response of the blood pressure to pressor electrolytes.

MICHAELS, Boston.

FUNDAMENTAL EFFECTS OF EPILEPTOGENOUS AGENTS UPON THE CENTRAL NERVOUS SYSTEM. E. A. SPIEGEL and M. SPIEGEL-ADOLF, Am. J. Psychiat. **92**:1145 (March) 1936.

The effect of changes in the state of hydration in the brain on the permeability of cell membranes in that organ is investigated by determining the "polarization index." This index is the difference between conductivity at high and that at low frequencies; a fall in this index indicates increased permeability, while a rise speaks for increased polarizability and, consequently, decreased permeability. The brains of fifty animals (calves, cats, rabbits and guinea-pigs) were used. In a few cases

experiments were performed on living animals under ether or dial anesthesia; in these cases the electrodes were inserted through small trephine holes. Most of the experiments, however, were carried out in vitro, the brains being studied almost immediately after death. Measurements were made on the lateral surfaces of the hemispheres, after the brain was symmetrically divided.

A brain placed in distilled water or alkaline or hypotonic salt solution undergoes swelling, and at the same time the polarization index falls; i. e., the permeability increases. The index was higher in nuclear tissues, such as the cortex and basal ganglia, than in zones of white matter, suggesting greater permeability in the white matter. The surfaces of the ganglion cells apparently play a large rôle in the phenomenon of polarization. It would thus appear that agents which produce swelling of the brain also increase permeability and that this is a reversible process, since the use of acids or hypertonic solutions may raise the polarization index again. A physiologic basis for the association between cerebral edema and cell permeability thus appears to be established, and the mechanism whereby convulsive reactivity is augmented during cerebral edema may be more clearly understood.

DAVIDSON, Newark, N. J.

ULCERATION IN THE DIGESTIVE TRACT OF THE DOG FOLLOWING INTRACRANIAL PROCEDURES. ALLEN D. KELLER, Arch. Path. **21**:127 (Feb.) 1936.

Cushing has pointed out the frequent association of gastro-intestinal disturbances and tumor of the hypothalamic region. In all his cases bleeding into the lumen and the gastric mucosa was prominent. He suggested that the gastro-intestinal changes were mediated by way of the vagus nerves. He presented convincing evidence that the central mechanism of the vagus nerve is represented in the brain stem as far cephalad as the hypothalamus.

Keller reports observations on the digestive tract of two hundred dogs in which lesions were made in the brain stem. Chronic animals were used. Hemorrhagic states ranging from pronounced blotchy hyperemia of the body of the stomach, with bleeding into the lumen, to more marked lesions in which the hyperemia had progressed to localized hemorrhages in the mucosa were encountered. Of twenty dogs in which the hemorrhagic state was precipitated, twelve died in twenty-four hours or less; four, in less than forty-eight hours, and the remaining four, within seventy-two hours after operation.

In nineteen dogs hemorrhage of the gastro-intestinal tract followed a lesion in the hypothalamic region; in the remaining instance it followed a transverse section at the middle level of the midbrain, which lacked only a millimeter or so medially of being a hemisection. In fourteen dogs the hypothalamic lesion passed bilaterally in a transverse direction through the anterior portion of the hypothalamus, i. e., at the level of the optic chiasm; in these dogs the caudal extent of the lesion varied from the cephalic tip of the chiasm to the caudal tip. In three instances the lesion was placed well back of the anterior portion of the hypothalamus, encroaching on the nuclei of the tuber and leaving the posterior portion of the hypothalamus intact. In one dog the leesion was placed longitudinally, separating the lateral and the medial hypothalamic nuclei on one side. In the remaining animals the precipitating lesion was a slanting hemisection of the brain stem so placed as to cut ventrally cephalad to the optic chiasm and dorsally just caudal to the thalamus.

In eighteen of the twenty dogs the lesion reached the third ventricle, so that the ventricular fluid had direct communication with the débris of the lesion. In certain of these animals blood entered the ventricle, as evidenced by the presence of clots. However, typical mucosal changes occurred after well delimited lesions, with no evidence of blood actually present in the ventricles. Two of the lesions did not extend to the ventricle. Of particular importance is the fact that typical hemorrhagic states were induced after lesions which had completely destroyed the anterior portion of the hypothalamus and encroached on the region of the tuber. In no instance was there evidence of increased intracranial pressure, such as would be indicated by intracranial hemorrhage or edema of the brain.

The character of the lesions placed in the present experiments does not permit conclusions concerning the specific nuclei involved in the hypothalamus. It is to be recalled, however, that the hemorrhagic states occurred spontaneously after complete destruction of the anterior portion of the hypothalamus, whereas craters were never encountered unless part of the anterior part of the hypothalamus was intact. This might suggest, particularly in the light of Beattie's exacting experiments, that the hemorrhagic states were precipitated by activation of the sympathetic outflow (posterior portion of the hypothalamus) and the craters by activation of the parasympathetic outflow (anterior portion of the hypothalamus).

WINKELMAN, Philadelphia.

HALIDE DISTRIBUTION IN BODY FLUIDS IN CHRONIC BROMIDE INTOXICATION. MORTON F. MASON, J. Biol. Chem. **113**:61, 1936.

Mason's purpose in this investigation was to study the distribution of bromide and chloride in man and dogs chronically intoxicated with bromide. Simultaneous observations were made on the distribution of these halides between the serum and the cells (erythrocytes), the spinal fluid, the urine, the saliva and the gastric juice, respectively. The ratio of distribution (e. g., bromide in the cells: bromide in the serum) is slightly higher for bromide than for chloride. It appears that the extra bromide in the cells does not displace its equivalent of chloride. The ratio of distribution for bromide between the serum and the spinal fluid is much greater than that for chloride. Treatment with sodium chloride increases further the value for the ratio of bromide distribution in patients. The replacement of chloride by bromide in the urine is less than that found simultaneously in the serum. It was not affected by diuresis or changes in the intake of sodium chloride.

PAGE, New York.

THE PROVITAMIN D OF HEAT-TREATED CHOLESTEROL. MILICENT L. HATHAWAY and DOROTHY E. LOBB, J. Biol. Chem. **113**:105, 1936.

Hathaway and Lobb have confirmed Waddell's observation that irradiated crude cholesterol (from the brain) is more effective in preventing rickets in chicks than irradiated ergosterol in an equivalent number of units. Purification of the crude cholesterol over the dibromide destroys the provitamin, but the same or a different provitamin D, effective for chicks, is found on heating this purified cholesterol. It seems probable that heat-treated cholesterol when irradiated produces a new form of vitamin D. It has properties, as shown by assay on chicks, more closely resembling those of the natural vitamin D of cod liver oil than those of the vitamin D formed by irradiation of ergosterol. From this work and that of Bills, the Kochs, Waddell and others, it is apparent that the problem of vitamin D is by no means solved.

PAGE, New York.

METAL CATALYSTS IN BIOLOGIC OXIDATIONS: II. TISSUE INHIBITORS. M. S. KHARASCH, R. R. LEGAULT, A. B. WILDER and R. W. GERARD, J. Biol. Chem. **113**:557, 1936.

The presence in tissue of specific inhibitors of metal-catalyzed oxidations of thioglycolic acid is reported. Thus, beef or chicken muscle yields extracts highly inhibitory to iron but somewhat acceleratory to copper and manganese catalysis. Extracts from chicken liver are neutral to iron, accelerate manganese and inhibit copper catalysis. In a few instances in which direct comparison was made, the intensity of the inhibition of copper catalysis by various extracts of liver paralleled their therapeutic value in the treatment of pernicious anemia. Liver extracts that failed to inhibit copper catalysis also failed to produce improvement in patients. This is part of an investigation the aim of which was to study the general problem of the rate at which tissue burns the substrate and frees energy. The authors believe that the critical factors in these reactions are the amount of active catalytic systems and the conditions determining their accessibility to the substrate and the degree of activity. Metal catalysis is considered in this paper.

PAGE, New York.

CORTICAL INNERVATION OF RESPIRATORY MOVEMENTS. SLOWING OF RESPIRATORY MOVEMENTS BY CEREBRAL STIMULATION. P. C. BUCY and T. J. CASE, J. Nerv. & Ment. Dis. **84**:156 (Aug.) 1936.

Bucy and Case have attempted to ascertain the area of the cortex from which changes in respiration can be elicited. Adult dogs were employed. All experiments were conducted with the animals under light ether anesthesia. In all six acceptable animals slowing and arrest of respiration were obtained by stimulation of an area of the coronal gyrus just ventral to the coronal sulcus and slightly posterior to the anterior end of this sulcus. This area lay just ventral to the anterior limb of the sigmoid gyrus. On only one occasion was comparable slowing obtained from any other region of the cerebral cortex. This was from a region about the anterior limb of the suprasylvian sulcus, but the slowing was less marked than from the site first mentioned. The intensity of the response varied with the depth of anesthesia. Deep anesthesia abolished all responses. The slowing of respiratory movements occurred promptly after stimulation and lasted after termination of stimulation for as long as thirty seconds. Hence the present work tends to confirm older work indicating that a definite cortical area is concerned with respiration.

HART, New York.

VITAMIN B_1 DEFICIENCY IN THE RAT'S BRAIN. J. R. O'BRIEN and R. A. PETERS, J. Physiol. **85**:454 (Dec.) 1935.

A study was made of the respiration in vitro of teased brain tissue from rats, both normal animals and those exhibiting neuritic symptoms of vitamin B_1 deficiency. The authors found that respiration in the brain of the avitaminous rat is increased by the addition of vitamin B_1; negligible effects occur with the normal animal. As in the pigeon, vitamin B_1 reduces the formation of abnormal amounts of pyruvate in the brain of the respiring avitaminous rat. It is noted that the symptoms of avitaminosis in the rat and the pigeon are central in origin and have essentially the same biochemical origin.

ALPERS, Philadelphia.

RÔLE OF THE BULBAR OLIVES. NATHALIE ZAND, Encéphale **31**:270, 1936.

In 1925 Zand suggested that the olives are the coordinating center of muscles concerned with erect station—or, in other words, the center of decerebrate rigidity. Experimental evidence for this concept was derived from decerebration of rabbits combined with destruction of one of the olives, either before or after decerebration. In both cases decerebrate rigidity was absent from the side of the body contralateral to the olive destroyed. A comparative study showed that the olives are best developed in animals which can hold the body vertically while resting on two limbs. Further confirmation was supplied by two cases of emprosthotonos, i. e., anterior flexion of the head, in man. Degeneration of the inferior poles of the olives was observed. This observation suggested a new hypothesis—that of a somatotopic arrangement such that the inferior pole of the olive is concerned with the upper segment of the body and vice versa.

In the present work the olives of rabbits were stimulated by the faradic current or by injections of distilled water, Ringer solution, paraffin or a 1:500 aqueous solution of strychnine nitrate. The last solution was found to be most effective. In each case the animal was killed and the site of penetration of the needle determined by microscopic examination. Two approaches to the olive were employed. One consisted of suboccipital puncture through the tissues of the neck. In the second method the atlanto-occipital membrane was incised and the needle inserted between the cuneate and the gracile bundle.

From these experiments the following conclusions were drawn: Stimulation of the olive results in contralateral rigidity of the extensor muscles; the somatotopic arrangement is such that the superior pole of the olive corresponds to the pelvic limb, the middle portion to the scapular limb and the inferior pole to the neck; stimulation of the "descending bundle of Deiters" has the same effects as that of the olive, but they are ipsilateral. In a few animals unilateral stimulation of the

bundle of Deiters resulted in bilateral rigidity. The relations between the olives and the system of Deiters' nucleus is not clear. Observations by Whiteaker and Alexander and by Tschernischeff indicated that degeneration of the olives accompanies that of the nuclei of Deiters. Zand suggests that the olives are subordinated to the stimulation of other centers, both inhibitory and exciting. Of these Deiters' nucleus is the principal one. If this is correct, stimulation of Deiters' system would be without effect on the extensor muscles after destruction of the corresponding olive. Experiments to test this hypothesis will soon be undertaken.

LIBER, New York.

ELECTRO-ENCEPHALOGRAMS IN MAN. HANS BERGER, Arch. f. Psychiat. **104**:678 (March) 1936.

Berger discusses a number of controversial points that have been raised in relationship to his publications on electro-encephalography. The contention that the beta waves are not limited in frequency to from 20 to 125 per second, as he originally suggested, is considered by him to be unjustified, because the reports of frequencies up to 1,000 per second must have been due either to superimposition of different waves one on the other or to accidental admixture of muscle action currents, especially of the temporal muscles. A further contention that the beta waves do not come from the cerebrum is countered by the fact that Berger has obtained these waves by means of electrodes that were inserted into the brain tissue itself and were insulated from other tissues.

The occurrence of varying frequencies of the alpha waves is related to the effects of certain pathologic conditions on these waves. Berger has obtained frequencies ranging from 5 to 20 per second in pathologic lesions. He considers the normal frequency to be about 10 per second. Anything much below that he associates with depressive effects, whereas frequencies above 10 a second are considered as indicative of excitatory stimuli. Frequencies below 10 were found in deteriorated epileptic patients, and those above 10, in excited patients with acute dementia paralytica. He states further that increased frequency of the alpha waves is found in normal persons when they are in a state of emotional excitement. He also discusses the problem of the origin of these waves, especially in relationship to Adrian's contention that they originate in the occipital lobe. Against that he brings the findings in experiments in which the electro-encephalograms were made simultaneously over different parts of the brain, with the result that although a number of alpha waves were in phase, some were out of phase. According to him, it is impossible to conceive that waves originating at one point only could, on the same record, be at some times in phase and at other times out of phase. Further proof that the waves originate in different parts of the cortex is found in cases of tumors of the brain, an instance of which he reports in this article.

MALAMUD, Iowa City.

THE MECHANISM OF FLACCID PARALYSIS IN CEREBRAL HEMIPLEGIA. I. SCHEINKER, Jahrb. f. Psychiat. u. Neurol. **53**:63, 1936.

In a man aged 39 there developed gradually signs of an expanding lesion in the right frontocentral region of the brain. Four months after the appearance of progressive flaccid left hemiparesis, craniotomy disclosed an inoperable tumor situated deep in the region indicated. After four weeks of relative comfort, severe symptoms of intracranial hypertension, with 6 diopters of papilledema, necessitated a second operation; the patient died on the following day—six months after onset of the illness. The significant findings relevant to Scheinker's thesis were: normal tonus of the paretic muscles at the onset of the disease; flaccid hemiparesis during the four weeks following the first operation; normal cutaneous sensibility, although the patient's mental condition was such that the examiner could not be certain as to the responses during the sensory examination; disturbance of sense of position of the toes of the left foot following the first operation, and absence of contracture of the affected limbs.

Necropsy revealed a carcinoma of the pancreas with cerebral metastases, the largest of which was in the frontocentral region of the right cerebral hemisphere. A second metastatic tumor was present in the right basal ganglia, the entire pallidum and part of the putamen being replaced by tumor tissue. Caudally, tumor nodules were observed in the region of the thalamus, with destruction of the ventrolateral portion of that ganglion.

After a critical review of the theories that thus far have been offered to explain flaccid paralysis, as well as contractures, in upper motor neuron lesions, Scheinker concludes that total flaccid cerebral hemiparesis is due to total interruption of the motor pathways descending from the cerebral cortex, associated with a lesion involving the extrapyramidal centers. In such cases neither contracture nor the stretch reflex (Foerster) occurs when the reflex arc is interrupted (*a*) by a lesion affecting the motor pathways which conduct impulses from the subcortical centers to the muscles or (*b*) by destruction of centripetal pathways or of their end-stations in the thalamus. KESCHNER, New York.

Neuropathology

MULTIPLE PRIMARY TUMORS OF THE BRAIN. C. B. COURVILLE, Am. J. Cancer **26**:703, 1936.

Almost every variety and combination of multiple intracranial tumors occur. In most cases the occurrence of tumors arising from two separate tissues is largely a matter of chance. On the other hand, a number of cases of multiple tumor of the meninges (meningioma), of the nerve roots (central neurofibromatosis) and of the brain (glioma) have been reported which suggest a predisposition to the formation of multiple tumor. In a review of the literature, 113 cases of what appear to be bona fide instances of multiple glioma have been identified and the essential observations tabulated. To this number 21 personally studied instances of multiple glioma have been added. In most cases the cerebral hemispheres were the seat of the multiple tumor. These cases may be grouped into three classes: (1) those in which both hemispheres were the seat of the tumor, symmetrical regions being affected in about half of the cases; (2) those in which the corpus callosum and one hemisphere were affected and (3) those in which one hemisphere alone was affected. Multiple glioma of the neuraxis, the ventricles or the cerebellum is much more rare. The individual growths vary considerably in size, degree of invasiveness and type of regressive changes. Growths of different size may be present in a given case, suggesting either a difference in their degree of malignancy or in their time of genesis. Solid, hemorrhagic and cystic growths may all be seen in a single case. In the majority of cases the tumor proves to be multiform glioblastoma. Multiple astrocytoma and other types are much more rare. In Courville's series, multiple astrocytoma was observed only in the cerebellum (vermis and lobe) and the thalamus. It is possible that other types of glioma may be multiple (ganglioglioma, etc.). The development of multiple independent growths is the only logical explanation for the widespread multiple tumor. In the case of small satellite growths about a larger growth, it is possible that the large tumor may "infect" or stimulate growth at the other foci (discontinuous growth). The distribution of the growths and the arrangement of anatomic structures seem to exclude the possibility of metastases by way of arterial or venous channels, the perivascular channels or the cerebrospinal fluid. FROM THE AUTHOR'S SUMMARY. [ARCH. PATH.]

TUMOR OF THE OPTIC NERVE. FREDERICK A. KIEHLE, Arch. Ophth. **15**:686 (April) 1936.

Primary tumor of the optic nerve is rare. The size of the growth varies from that of a small localized thickening to a mass that fills the orbit and produces extreme exophthalmos. Ophthalmologically, this tumor is usually accompanied

by neuritis of the postbulbar type, with marked venous engorgement. Later, evidences of atrophy of the optic nerve appear. Kiehle calls attention to the possible mesoblastic origin of the tumor. He asks that it no longer be called a neuroma, since Parsons stated that true neuroma "does not occur in that portion of the central nervous system of which the optic nerve is a part."

SPAETH, Philadelphia.

PRIMARY TUMOR OF THE OPTIC NERVE. TULLOS O. COSTON, Arch. Ophth. **15**:696 (April) 1936.

Coston discusses primary tumor of the optic nerve and reports a case in which microscopic examination revealed a dural endothelioma of the optic nerve, with invasion of the optic disk and atrophy. The case is unusual, for the extension of the growth to the disk was recognized opthalmoscopically and the diagnosis was proved subsequently by histologic examination. Enucleation was performed, and the patient has continued to be well for a year.

Primary tumor of the optic nerve is infrequent. In 80 per cent of 300 cases investigated by Verhoeff, the tumor was glioma; in 17 per cent, endothelioma or meningioma, and in 3 per cent, fibroma. In most cases glioma arises from the intra-orbital portion of the nerve. In at least 75 per cent the tumor appears before the age of 5 years, and in the major portion of the remaining 25 per cent, before the age of 20. Coston reports Verhoeff's observations in eight cases of endothelioma. In no case did the tumor arise intra-orbitally. It does not metastasize. The damage is by extension of the growth.

SPAETH, Philadelphia.

NEURO-EPITHELIAL CYST OF THE THIRD VENTRICLE. DONALD J. REHBOCK, Arch. Path. **21**:524 (April) 1936.

The neuro-epithelial cyst, sometimes less correctly called the colloid cyst, is a benign primary tumor of the third ventricle of the brain. Only fifty-two authentic cases have been described. This paper reports three additional cases. The neuro-epithelial cyst arises in a congenital defect. The exact point of origin is at present disputed; the cyst may be derived from a rudimentary ependymal or choroid structure. It is attached by a pedicle to the roof of the third ventricle and consists of a thin epithelial wall and a content of homogeneous acidophilic material, which is probably pseudomucin.

The incidence is higher in males (63 per cent) than in females, and persons in whom the lesion occurs are usually between 20 and 50 years of age. Only one of the cases reported occurred in a person under 18 years of age.

In 84 per cent of the cases symptoms were present for one month or more, and in 51 per cent, for no longer than one year; in only 14 per cent did death occur subsequent to the first observed attack. The characteristic signs and symptoms are produced by intermittent acute obstruction of the foramina of Monro or the third ventricle by the cyst. This causes paroxysms of severe headache in the frontal region, nausea, vomiting and papilledema. Relief or exaggeration of symptoms occurs with changes of posture. Symptoms and signs of diencephalic involvement have been present in many cases. No correct clinical diagnosis has been made. The treatment is surgical removal. Twelve operations with nine cures have been reported. The operation of choice is an approach through the lateral ventricle by way of the frontal lobe and removal of the tumor through the foramen of Monro.

WINKELMAN, Philadelphia.

RELATION OF GLIOMA OF THE LEPTOMENINGES TO NEUROGLIA NESTS: REPORT OF A CASE OF ASTROCYTOMA OF THE LEPTOMENINGES. ORVILLE T. BAILEY, Arch. Path. **21**:584 (May) 1936.

Considerable evidence has been published in recent years to support the conception of the derivation of the leptomeninges from the neural crest. Some authors have referred, therefore, to all meningeal tumors as glioma and have classified

the tumors as neurofibroma, which has been regarded as a peripheral glioma. The common tumor of the leptomeninges, usually called meningioma, has little in common with the glial tumor arising within the brain substance.

This paper calls attention to an unusual tumor of the leptomeninges which is identical in histologic appearance with the glioma of the brain substance and discusses the possible relationship of such a tumor to neuroglial nests in the meninges. This tumor is not identical with so-called gliomatosis of the meninges, in which there is seeding of the meninges from a glioma arising in the brain substance, or to the sarcomatous tumor of the leptomeninges.

Bailey concludes that a small group of gliomas of the leptomeninges are situated in the subarachnoid space. The presence of neuroglial nests in these locations offers a ready explanation of their histogenesis. The case of Bailey and the cases reported in the literature were all instances of astrocytoma. Theoretically, it should be possible for ependymoma to occur in the leptomeninges, because of the occasional presence of ependymal canals in the nests of neuroglial tissue. This neoplasm represents a specific type of tumor of the leptomeninges.

Neuroglial nests in the meninges offer the most probable explanation of the histogenesis of glioma of the leptomeninges. These are anomalous inclusions of neuroglia in the subarachnoid space. They may occur in instances of extensive congenital malformations of the central nervous system and have also been encountered without other anomalies of the brain or spinal cord.

WINKELMAN, Philadelphia.

THE AETIOLOGY OF SUBDURAL HEMATOMA. J. A. HANNAH, J. Nerv. & Ment. Dis. **84**:169 (Aug.) 1936.

Subdural hematoma is characterized by a history of trauma followed by a quiescent period of from a few weeks to years, during which increased intracranial pressure with neurologic and mental symptoms occurs. At autopsy a hematoma is observed under the fibrous layers of the dura, at the site of a dense capillary network. This layer of capillaries is separated from the endothelial lining of the dura by a third layer of fibrous tissue. Contrary to the usual conception, the dura is richer in vessels than seems necessary for its function. It is supplied by from twelve to fifteen arteries, which form the dense network between the middle and the inner layer. Hannah made injections of citrated blood into the outer layers of fresh dura and found that invariably the blood found its way toward the inner surface of the dura, where it raised blebs. This simple experiment proves the presence of a third layer of the dura. The false membrane is the result of reaction to intradural hemorrhage and does not grow around the clot. In view of these observations, it is suggested that the best name for the condition is "hematoma durae matris," originally employed by Virchow.

HART, New York.

ACUTE CYSTIC PNEUMOCOCCIC MENINGITIS IN A PATIENT WITH DEMENTIA PARALYTICA. L. MARCHAND, P. PETIT and J. FORTINEAU, Ann. méd.-psychol. **94** (pt. 1) : 754 (May) 1936.

The authors report a case of early dementia paralytica with typical mental changes, dysarthria, Argyll Robertson pupils, positive serologic reactions of the blood and spinal fluid and a benzoin curve of 222222222221000. A few weeks after the patient was admitted to the hospital, bronchopneumonia complicated by right hemiparesis developed and was followed by a series of convulsions involving the right side of the body. Although the usual signs of meningitis were absent, lumbar puncture yielded slightly xanthochromic purulent fluid, with 850 white cells, 95 per cent of which were polymorphonuclears, a protein content of 280 mg. per hundred cubic centimeters and a benzoin curve of 222222200222222. Serologic reactions remained positive. The patient died in convulsions. Autopsy revealed widespread purulent infiltration of the pia, especially over the anterior portion of the cerebral hemispheres, along the sylvian fissures and about the cerebral peduncles and the

stalk of the pituitary. Over the left hemisphere there was a closed pocket of yellow pus encapsulated by a thick fibrous membrane, which was organized like the membrane of a subdural hematoma. The purulent meningeal infiltration contained numerous pneumococci. The cerebral parenchyma showed lesions characteristic of dementia paralytica. The parenchyma was free from pneumococci, which were confined strictly to the pia-arachnoid. The authors cite several other instances of purulent meningitis in association with dementia paralytica and point out that the specific inflammatory process involving the meninges does not appear to be an obstacle to the development of acute meningitis; in fact, it seems to make the pia even more sensitive to superimposed infection.

YAKOVLEV, Waltham, Mass.

ATYPICAL VARIETIES OF MENINGIOMA: MULTIPLE, RECURRENT AND INFILTRATING TUMORS. D. PETIT-DUTAILLIS and L. ECTORS, Presse méd. **44**:486 (March 21) 1936.

Meningomas of the arachnoid are usually solitary tumors, well encapsulated and situated on the surface of the brain, which they compress without invading the cerebral tissue proper. However, there are exceptions to this rule. In rare instances the tumors are observed within the brain tissue, independent of the meninges. Cases of multiple meningiomas have been reported. The authors found twenty-eight instances of this type in the literature and included two cases of their own. The meningiomas may be associated with other types of tumor of the nervous system, especially acoustic neurinoma and neurofibroma. One must be aware of the possibility of multiple meningiomas. The authors cite instances in which operation on an apparently single meningioma failed to benefit the patient because the concurrent tumors were missed at operation, either on account of their small size or their remoteness from the operative field. True recurrence of a meningioma is rare. The authors report in detail a case in which the focal symptoms recurred a few months after the removal of a meningioma adherent to the dura and embedded in the brain at the middle portion of the right rolandic area; three years later a second operation disclosed a meningioma situated at the upper portion of the rolandic area on the same side, involving the falx and the wall of the superior longitudinal sinus. The tumor was successfully removed, and the patient made a lasting recovery. The recurrence of a meningioma may be due to incomplete excision of the tumor, when the latter involves a venous sinus, or insemination of the meninges with neoplastic elements while incising the capsule. However, in the majority of instances of recurrence these explanations are inadequate. The case reported by the authors was not one of true recurrence of a meningioma; two tumors developed in succession and independently. The authors state that most cases reported in the literature as instances of recurrent meningioma are in reality cases of multiple meningiomas. They advise careful inspection of the meninges around the tumor during operation, in order to detect and remove other tumors, which may consist of small nodules, easily overlooked, and which later may give rise to "pseudorecurrences." A meningioma may not remain confined to the subarachnoid space but may involve the dura more or less extensively and propagate along the diploic veins and haversian canals into the skull, causing both osteoporotic and osteohyperplastic changes in the bone. In the majority of such cases a permanent cure may be obtained by autoclaving the involved bone flap (Vincent). A more serious complication is the spread of the tumor into the venous sinuses. In most instances of this sort the tumor involves only the superficial layers of the wall of the sinus. However, true invasion of the sinus leading to thrombosis with neoplastic elements has been reported, and in exceptional cases the meningioma has developed as an exceedingly malignant tumor of the hemangioblastic variety, no longer encapsulated but infiltrating the surrounding structure and diffusely invading the bone. The authors report in detail a case of such an infiltrating meningioma of hemangioblastic type, histologically verified. In a patient aged 61 at the time of operation, the symptoms of intracranial tumor developed and progressed in the course of five years. They consisted at first of protrusion of the left eyeball, without visual disturbances or

headache. Later, convulsions began to occur at irregular intervals, and eventually slight headache developed. Examination revealed no abnormalities. Lumbar puncture revealed nothing abnormal. The diagnosis was made mainly on the evidence of local pain, parchment-like crepitation and bulging in the left parietal bone. The roentgenogram showed rarefying osteitis, resembling Paget's disease and involving the parietal, temporal and frontal bones on the left. Histologic examination of a piece of the bone removed from the affected area demonstrated a beginning fibro-endothelioma developing from the blood vessels of the diploe. Operation revealed a tumor situated in the left parietal region, invading the skull and dura, extending up to the superior longitudinal sinus and extensively infiltrating the surrounding brain tissue. To the naked eye there was no evidence of any cleavage between the neoplastic and the cerebral tissue. The tumor was removed in fragments by electrocoagulation. The patient made a good recovery and left the hospital twenty days after operation. He remained well for six months; the symptoms then recurred, and four months later he died a few hours after a convulsion. Histologic examination of the fragments of tumor and bone removed at operation showed that the neoplastic infiltration invaded the bone far beyond the limits of the intracranial tumor proper. The outer and inner tables were destroyed; the bone of the cranial wall was hyperplastic and in places was 3 cm. thick. The invading neoplastic elements were fibroblasts, arranged in characteristic whorls resembling an onion. The neoplastic elements within the brain were those of a young fibro-endothelioma and had the same histologic characters as the fibroblasts in the invaded skull bone. The delimitation between the neoplastic and the cerebral tissue was extremely variable; in many places fragments of capsule consisting of richly vascular meningeal connective tissue fibers, as in typical meningioma, were observed, while in other places the neoplastic whorls were embedded in the cerebral tissue. The tumor began as an ordinary benign fibro-endothelioma and in the course of five years became malignant by losing its capsule and infiltrating the meninges, the skull and the brain. The atypical varieties of meningioma discussed, rare as they are, show, nevertheless, that these tumors are not always benign, solitary, encapsulated, nonrecurrent and noninfiltrating.

YAKOVLEV, Waltham, Mass.

VARIABILITY OF PERIVASCULAR REACTIONS IN DIFFERENT TYPES OF ENCEPHALITIS. IVAN BERTRAND and KENJI MIYASHITA, Presse méd. **44**:491 (March 21) 1936.

Perivascular infiltration, with glial proliferation and neuronophagia, represents the essential manifestation of encephalitis. The authors divide the encephalitides into two main groups: the demyelinating and the nondemyelinating forms. In the first group they discuss disseminated encephalomyelitis (acute multiple sclerosis), leuko-encephalitides (diffuse scleroses) and encephalitides following eruptive fevers. The perivascular reaction in acute multiple sclerosis is characterized by the prevalence of lymphocytes and especially of granular cells, the latter resulting from local transformation of the proliferated adventitial histiocytes; the fibrocytes of the adventitia are enormously swollen and contain a few lipid inclusions; they are in contrast with the intact endothelial cells; the plasmocytes are few and show little activity; the process is one of rapid evolution and may lead to liquefaction of the parenchyma.

In diffuse scleroses, whether inflammatory, degenerative or blastomatous, the perivascular reaction is always observed. In a case of diffuse familial sclerosis studied by the authors, there were diffuse systematization of the lesions in the white matter, a tendency to form perivascular lacunae filled with granular bodies and rare lymphocytes and a tinctorial reaction of the lipids filling the granular bodies scattered in the parenchyma which differed from that of lipids contained in the spongiocytes of the adventitia.

In encephalitis following eruptive fevers (measles and vaccination) the perivascular reaction is highly typical and is characterized essentially by the perivenular arrangement in the white matter of the cerebral convolutions, by widespread thromboses, sometimes involving large meningeal blood vessels and venous sinuses,

and by spotty demyelinization in the form of narrow halos around each infiltrated and thrombosed blood vessel. This is in contrast with the widespread blotchy and confluent demyelinization characteristic of multiple and diffuse sclerosis. The perivascular infiltration consists chiefly of cells of hematogenous origin—large mononuclears and neutrophils; lymphocytes and plasmocytes are rare. This type of reaction suggests an aseptic allergic process rather than true encephalitis.

In encephalitis lethargica the small veins and capillaries in the gray matter of the brain stem are especially affected; the peculiar feature of the perivascular reaction between the gray and the white matter is that the portion of the blood vessel facing the gray matter usually shows a thick infiltration, while the portion facing the white matter remains free; the prevalence of lymphocytes is striking; plasmocytes are rare; polymorphonuclears are exceptional; large mononuclear cells and a few vacuolated macrophages filled with débris are also seen. In encephalitis associated with rabies the authors distinguish two types of perivascular reaction: in one, usually seen in the cerebral hemispheres, the infiltration consists chiefly of proliferated adventitial cells of histiocytic origin, associated with a few lymphocytes, rare polymorphonuclears and mast cells. The second type occurs mostly in the gray matter of the medulla; in this the adventitial cells are less numerous; the infiltration consists mainly of polymorphonuclears, which often penetrate the glial perivascular screen and invade the surrounding parenchyma; the reaction of the second type represents a more advanced, necrotic stage of a particularly acute inflammation. In the encephalitis known as Borna disease and in the encephalitis seen in young dogs, the perivascular reaction resembles that in encephalitis lethargica. In Borna disease the infiltration consists mainly of lymphocytes associated with plasmocytes, large mononuclears, a few granular bodies and various transitional forms of lymphocytes; the endothelial cells and most of the adventitial cells are hypertrophied; the infiltration is confined to the adventitia; the perivascular spaces are distended, owing to edema, but contain no cells, and the parenchyma is never invaded. In the encephalitis of young dogs (Carré's disease), the infiltration around the large vessels consists chiefly of lymphocytes, while that around the capillaries contains many plasmocytes which are attached to the wall of the vessel in an arrangement resembling that of epithelium; the lesion prevails in the gray matter and affects especially the midbrain. In encephalitis, produced experimentally with herpes virus the infiltration during the early stages consists chiefly of polymorphonuclears, but later monocytes become prevalent; plasmocytes are absent; the parenchyma is frequently invaded. In encephalitis associated with torula infection the yeast germs are easily recognized by their double contour; some of them are free in the perivascular spaces, and others are taken up by macrophages; the infiltration is essentially lymphocytic; neither plasmocytes nor polymorphonuclears are present. The authors point out the interest of a minute study of perivascular reactions for the classification and diagnosis of the encephalitides. They emphasize that in encephalitides the inflammatory reaction is strictly perivascular; the endothelium usually remains intact. This shows that a virus is not the sole cause of the perivascular infiltration. They believe that as the result of parenchymatous lesions caused by the virus, there are formed toxic products of protein disintegration (polypeptides) which are eliminated through the perivascular spaces, irritate the adventitia and lead to the characteristic perivascular inflammatory reaction. YAKOVLEV, Waltham, Mass.

ANATOMIC AND PATHOLOGIC FEATURES OF MONGOLOIDISM. W. H. STEFKO and L. IVANOWA, Bull. Soc. roumaine de neurol. **26**:57, 1935.

The pathologic changes in three mongoloid idiots aged 3, 9 and 10 years, respectively, are described. The thyroid gland, the lungs and the adrenal glands showed immature structure, particularly the thyroid, which was described as fetal. The gyri of the cerebral cortex, particularly the precentral, postcentral and central, were all flattened. Anastomoses and supplementary sulci were not developed. The occipital lobe presented anomalies. The sulcus occipitalis transversus and

the sulcus parieto-occipitalis were deep and joined the sulcus intraparietalis, thus delimiting entirely the occipital lobe. Cyto-architectonic study showed in area praecentralis gigantopyramidalis lack of development of layers V and VI and, to some extent, of layer I. The giant pyramidal cells were round. In area frontalis agranularis, layers I and VI were thick. Layer III was thinner than layer I, and its cells were irregularly disposed. In area frontalis intermedia layer III was broad, and layers V and VI were not distinguishable from one another, both having the structure of layer V. Area frontalis granularis showed considerable lack of development; layer VI, in particular, was two-fifths the normal thickness. In all the areas of the inferior frontal region, the thickness of the cortex was diminished. Many of these peculiarities, both of the brain and of other organs, resemble those of adult members of the mongolian race, whose development in certain respects is arrested at a level corresponding to that of the European age level of about 5 years. The authors believe that mongoloidism is a distinct genotype.

LIBER, New York.

Diseases of the Brain

UNILATERAL EXOPHTHALMOS PRODUCED BY A MENINGIOMA OF THE MIDDLE CRANIAL FOSSA. MARTIN COHEN and JOHN E. SCARFF, Arch. Ophth. **13**:771 (May) 1935.

Cohen and Scarff describe a case of unilateral exophthalmos produced by a meningioma of the middle cranial fossa. The exophthalmos was slow in developing, was progressive and was associated with ophthalmoplegia, with primary atrophy of the optic nerve and thickening of the posterior orbital plate on the side of the exophthalmos. This group of signs and symptoms seems to constitute a clinical and pathologic syndrome produced by a meningioma, i. e., a fibroblastoma of the middle cranial fossa.

SPAETH, Philadelphia.

PRIMARY TUMOR OF THE OPTIC NERVE. GAYLE H. MEHNEY, Arch. Ophth. **16**:95 (July) 1936.

Mehney presents three cases of primary tumor of the optic nerve, calling attention to the rarity of the condition, the possible changes in the fundus and the prognosis. If the intra-orbital portion of the nerve is involved and the tumor can be eradicated completely, prognosis for life is good. If the intracranial portion of the nerve is affected, the prognosis for life is poor, even though all the tumor can be removed with the nerve at enucleation.

The tumor in case 1 was a spongioblastoma. The patient has continued in good health for somewhat less than two years since enucleation was done. The tumor in case 2 was also a spongioblastoma, and the child has remained well and healthy for over three years. In case 3 there was bitemporal hemianopia, with evident intracranial invasion. A tentative diagnosis of pituitary tumor, was made, but at operation a tumor was observed arising from the left optic nerve, which was entirely replaced with neoplastic tissue nearly up to from 1.5 to 2 mm. from the optic foramen. The patient did not recover consciousness and died twenty-four hours later. A diagnosis of spongioblastoma was made also in this man.

These three cases emphasize the difference in diagnosis and prognosis of intra-orbital as compared with intracranial nerve tumor.

SPAETH, Philadelphia.

SOME OBSERVATIONS CONCERNING THE RELATION OF HANDEDNESS TO THE LANGUAGE MECHANISM. E. C. CHESHER, Bull. Neurol. Inst. New York **4**:556, 1936.

Chesher studied 240 patients with lesions in the language zone of one of the cerebral hemispheres. In 164 persons the location of the lesion was verified by at least two of the following procedures: air studies, operation or postmortem examination. The patients fell into three groups: Group I. Eighty-nine persons

with a discrete lesion within the language zone of the left cerebral hemisphere. All but 1 of these patients were aphasic, and all but this patient were right handed.

Group II. Sixty-eight patients with a discrete lesion in the language zone of the right cerebral hemisphere. All but 2 of these persons were right handed, and none were aphasic. The 2 left-handed persons in this group were aphasic.

Group III. Nine patients with histories of mixed motor preferences, i. e., an equally high degree of skill in either hand for any given act. These persons exhibited aphasic disturbances, regardless of the laterality of the lesion in the language zone. The view is advanced that in persons with mixed motor preferences the language mechanism is unilateralized, so that a lesion on either side can produce aphasia.

KUBITSCHEK, St. Louis.

THE RELATIONSHIP OF INTELLECT TO SPEECH DEFECT IN APHASIC PATIENTS. FOSTER KENNEDY and ALEXANDER WOLF, J. Nerv. & Ment. Dis. **84**:125 (Aug.) 1936.

The peripheral organs of speech, bilaterally innervated, eventually come under the control of one side of the brain, the left cortex. The theories of explanation are legion, but Dareste's theory of the more frequent attachment of the embryos to the uterus by the left side seems to Kennedy and Wolf to be the most convincing. At some period of childhood the right hand usually exhibits a greater capacity for finer adjustments and coordinations than the left. The gradual shifting of the center of speech to the left cerebrum, to the neglect of the right, as the child becomes adult may account for the increasing difficulty in learning and memorizing with age. At the same time, intellectual progress seems to depend on this concentration of the powers formerly divided between the two hemispheres, while, conversely, an attempt to force a child who is left handed to write with the right hand splits the representation of the speech areas and retards intellectual progress.

Kennedy and Wolf find that such generalizations as "the brain functions as a whole" tend to confuse diagnosis and therapy. A definite tendency to localization of functions exists and must be recognized. Thus, discrete lesions in front of the fissure of Rolando produce asphasia which is mainly motor. If the lesion is higher up, near the hand representation, there may be isolated agraphia. Morbid processes behind the rolandic fissure result in sensory aphasia of an auditory and anomic type when below the fissure of Sylvius, and of a visual nature when situated posteriorly at the parieto-occipitotemporal junction.

Kennedy and Wolf believe that there is a distinction between intellectual defect and aphasia, that thought is possible without speech or words and that defective speech can exist as something apart from intelligence, ideation, attention, memory and powers of association. As proof, they cite the case of a judge who, though suffering from aphasia which he discovered only when he attempted to speak, was able to reflect clearly. Weisenburg found that aphasic patients succeed relatively better in nonlanguage than in language performances. Defects in immediate recollection (symbolization) are not incompatible with unconscious production during casual conversations. Intellectual defects frequently occur with aphasia, however, and as Moutier has indicated, the degree of physical deterioration resulting from lesions in Wernicke's area is proportional to the size of the lesions in the zone, apparently because lesions of the largest size cause rupture of association paths and consequent reduction in brain integration. Even if there is no intellectual defect in aphasia, there is bound to be some later if the aphasia continues, because the man who cannot read or understand loses contact with his fellows and his environment and eventually shows deterioration.

Apraxic symptoms are usually found with extensive generalized lesions of the brain, in which the disturbance is large enough to implicate intellectual processes, owing to rupture of integrating association tracts. In clearcut cases of aphasia which results from small lesions there is rarely any apraxia, and mental function is commonly intact. The apraxic person who tries to smoke his tooth-brush and

clean his teeth with his pencil is suffering no longer from simple loss of power of symbolization but from real deterioration of the perceptive and associative faculty. Some evidence tends to localize the morbid changes producing apraxia in the frontal lobe, particularly in the first and second frontal convolution on the left. However, they are common also in disturbances affecting the remainder of the homolateral cortex surrounding the speech centers.

HART, New York.

THE DISORDERS OF MOTOR FUNCTION FOLLOWING AN ABLATION OF PART OF THE "LEG AREA" OF THE CORTEX IN MAN. F. M. R. WALSHE, Brain **58**:81, 1935.

An opportunity presented itself to study the effects of pure ablation of the "motor cortex" in the special sense of Fulton—one to which it could not be objected that the lesion encroached on Fulton's "premotor cortex." An intelligent girl aged 11 gave a history of convulsions of the left foot and leg of four years' duration. At times the left arm and the right extremities were involved to a less degree. Examination revealed no abnormal physical signs in the nervous system; the left leg was normal in every respect. On one occasion after an attack a transient extensor plantar response was obtained in the left foot. The attacks became more frequent and severe and transient periods of weakness of both arms and legs ensued. Examination shortly after an attack revealed increased tendon jerks in the left leg and a tendency to ankle clonus. There was a defect of postural sensibility in the left toes. Operation was performed, and the area from which movements of the foot and toes could be elicited was excised. Histologic examination of the excised tissue disclosed numerous Betz cells, proving that the frontal limits of the area gigantopyramidalis were not transgressed. The immediate postoperative picture and the clinical appearance fifty days after operation corresponded exactly with the syndrome described by Leyton and Sherrington in the chimpanzee and by Horsley in man and corresponded also to the picture of partial hemiplegia given by Hughlings Jackson in respect to the loss of movement. This syndrome may be summarized as follows: The immediate result was widespread paralysis of movements of the affected limb, the special and varied movements of the distal part of the limb being most severely paralyzed. The large and simple movements of the proximal part of the limb recovered early and completely, the special and more varied movements of the distal part recovering more slowly and less completely, so that some were permanently lost or impaired. Hypertonus developed in the most severely paralyzed parts of the limb, and the tendon jerks became and remained increased. This syndrome is attributed by Fulton to a lesion of the "premotor cortex" and of its hypothetic extrapyramidal projection system. It does not resemble Fulton's "syndrome of the motor cortex," which Walshe concludes has no real existence.

With the single exception of "forced grasping," Walshe concludes that Fulton's "syndrome of the premotor cortex" in man is in reality a syndrome of the true motor cortex and has nothing to do with a histologically and physiologically differentiated premotor cortex and its extrapyramidal projection system.

SALL, Philadelphia.

A DISEASE PROCESS RESEMBLING AMYOTROPHIC LATERAL SCLEROSIS WITH MENTAL SYMPTOMS. EVA TEICHMAN, Ztschr. f. d. ges. Neurol. u. Psychiat. **154**:32 (Oct.) 1935.

A musician aged 43 was admitted to the psychopathic ward on April 21, 1934. His past history was without significance, except for an operation for gastric ulcer and exemption from army service because of heart disease. For a year he had complained of palpitation and headache. Dyspnea was also present. He was admitted to the psychopathic ward in 1933 because of depression with suicidal tendencies. At that time insomnia, dizziness and unsteadiness of gait were present. There were weakness of the left side of the body, with a Babinski sign on the left, and Rossolimo and Mendel-Bechterew reflexes bilaterally. The diagnosis at the time of his discharge in January 1934 was multiple sclerosis.

Three months later the patient became much worse and was readmitted. At this time he was hardly able to walk; vision was poor, and he was irrational for a few weeks, with repeated suicidal threats. He was confused and restless. There was paresis of upward gaze; the small muscles of the hand were atrophied; there were mild hypotonia of all muscles and an inconstant Babinski sign on the right, but no sensory changes. The spinal fluid was normal, and the ocular fundi showed no significant changes. The patient remained restless and would not stay in bed. He thought he was being burnt and complained of the presence of smoke in the room. He repeatedly demanded a revolver with which to shoot himself and chase away alleged persecutors. He felt that persons were making fun of him. Examination four days after readmission to the hospital showed a Babinski sign bilaterally and *marche à petits pas,* with spastic paretic gait. During his stay in the hospital, the pupils were noted to be sluggish to light and in accommodation, and there was mild paresis of conjugate gaze to the left; peripheral facial palsy was recorded on the left, with dysarthria but no fibrillations of the tongue; the superficial reflexes were not elicited; there was an incomplete reaction of degeneration of the muscles of the hands and feet.

Histologic examination of the central nervous system showed diffuse ganglionic disease, especially of the larger cells. The earliest change seemed to be swelling of the cell and tigrolysis, with progressive breaking up of the cytoplasm and of the nucleus. The white matter was also extensively involved. A diffuse glial reaction was present in the form of massing of glia cells, with occasional formation of rosettes. There were widespread hyaline degeneration of the blood vessels and irregularly distributed perivascular lymphocytic infiltrations, especially in the medulla oblongata and the spinal cord. Marked thickening of the meninges was present, notably over the hemisphere, with edema of the underlying cortex. The disease process seemed oldest in the cortex and more recent in the bulb and the cord.

The anatomic changes were not strictly limited to systems, nor were the cell changes those of amyotrophic lateral sclerosis. The similarity between this disease and amyotrophic lateral sclerosis is entirely clinical. The type of glial response in this case is not encountered in amyotrophic lateral sclerosis.

Teichman suggests antointoxication as a possible cause of this obscure disease process, which is degenerative and inflammatory in nature. The disorder in gastro-intestinal function following the operation for gastric ulcer may have been an important etiologic factor. The presence of definite secondary anemia supports that hypothesis. The histologic observations of Alexander and Wu on the effect of acute and chronic gastro-intestinal disorders on the nervous system were similar to those noted in this case. This type of condition must be separated from amyotrophic lateral sclerosis and can be designated as chronic encephalomyelopathy, with a tendency to greater involvement of the motor cells and fibers.

SAVITSKY, New York.

Peripheral and Cranial Nerves

NEURITIC MANIFESTATIONS IN DIABETES MELLITUS. WILLIAM R. JORDAN, Arch. Int. Med. **57**:307 (Feb.) 1936.

Jordan examined two hundred and twenty-six patients suffering from diabetes complicated by peripheral neuritis. The forms of the disease are divisible into three groups: hyperglycemic (in 13 per cent of the patients), pure neuritic (in 52 per cent) and degenerative (in 35 per cent). The hyperglycemic group is defined as that which embraces the mild neuritides bearing some relationship to the hyperglycemia, in which symptoms tend to diminish as the diabetes is controlled. The neuritic group includes forms in which the neuritis is stubborn and extensive, while the degenerative type embraces conditions with a circulatory or an arteriosclerotic basis. In the hyperglycemic type the usual site of involvement is the lower extremity, and the outstanding symptoms are pain and cramps, which are

worse at night. There is little arteriosclerosis and the symptoms appear when the diabetes is uncontrolled, tending to vanish as the blood sugar is restored to normal. No special treatment of the neuritis is required, as the pain and cramps are controllable by any measures which control the underlying diabetes.

In the neuritic type pain is severe, and paresthesias, changes in the reflexes, areas of muscular weakness and scattered neurologic signs usually develop. Pain is worse at night and improves when the patient walks. In most cases the tendon reflexes are diminished or absent. Muscular weakness is found in most cases; there may be complete paralysis of a muscle group, although usually there is only paresis. Atrophy is often noted. Tenderness, hyperesthesia and alterations in objective cutaneous sensibility are found in slightly more than half of the cases. Little alteration in position sense is found, and ataxia is rare. Patients in this group are often unstable, restless and depressed. The keystone of therapy is intensive treatment for the diabetes. The diet should be as rich as possible. If the neuritis develops shortly after the initiation of treatment with insulin, the brand of insulin should be changed, as in some cases sensitiveness to the insulin solvent may account for the disorder. Pain is relieved best by heat, which is applied in the form of warm baths or an electric baker. Massage, Buerger's exercises and a program of alternating rest and exercise should all be tried.

In the degenerative type the onset is insidious. In most cases the extremities are involved, although pupillary changes are also frequent. There are paresthesias, cramps and pain—all worse at night. Among the neurologic findings are changes in reflexes, atrophies, weakness of the anal sphincter, tenderness of the muscles and areas of hyperesthesia. In every case some degree of arteriosclerosis is found. The course is prolonged, and the symptoms may persist. Heat is a valuable anodyne but must be applied with care because of the danger of burns. The electric baker is advised. Meticulous care must be taken in trimming nails, corns and calluses. Buerger's exercises should be used in all cases. DAVIDSON, Newark, N. J.

SURGICAL REPAIR OF THE FACIAL NERVE. ROBERT CARSON MARTIN, Arch. Otolaryng. **23**:458 (April) 1936.

The facial nerve may be repaired by direct anastomosis, homogenous graft or simple decompression. The time to operate varies with the type of case. If the nerve has been severed, the operation should be done at once. If the cause of the paralysis is not known, it is usually advisable to wait for from six to eight months, because in many cases recovery is spontaneous. While waiting for operation, it is important to strap the muscles so that they do not become stretched. Electrical stimulation is considered valueless by some authors. Massage may do harm by stretching the muscles and, after operation on the nerve, may pull the ends of the nerve apart. Reeducation before the mirror is beneficial. Martin reports a case of end to end anastomosis, a case of neurolysis and a case of nerve graft of the facial nerve, detailed records of which are given.

In the first case, the paralysis was noted on recovery from simple mastoidectomy. After a year a modified radical mastoidectomy was performed; the neuroma of the proximal end and the frayed distal margin of the nerve were removed and the two ends placed in apposition. Recovery began in seven months, and the face was normal in fourteen months, except for emotional control. In the second case the patient was injured in the course of mastoidectomy. Forty-one days later a second operation was performed; the nerve was observed to be exposed in its posterolateral surface in the upper vertical portion near the antrum, for an area of 0.5 cm. in length. The area was covered by fibrous tissue. Constriction of the nerve was demonstrated by injection of sodium chloride into the tissue. Three months later there was good return of function in all but the frontalis muscle. The function of the chorda tympani nerve was destroyed, as this nerve was severed when the facial nerve was lifted from its bed. Emotional control was poor, but reeducation was not carried out. In the third case the nerve was injured in the course of a radical mastoidectomy. For three months

following the operation, there was some twitching of the facial muscles, after which there was no further disturbance except that the right eye could not be closed and drooping of the right corner of the mouth was so marked that the patient ate with difficulty. The nerve was degenerated in the neighborhood of a cholesteatoma. A graft of the saphenous nerve was inserted, after the method of Ballance. The patient did not cooperate, and after eleven months he could twitch only the corner of his mouth.

HUNTER, Philadelphia.

PROGRESSIVE FAMILIAL HYPERTROPHIC NEURITIS (DEJERINE-SOTTAS). ERIC L. COOPER, Brit. M. J. **1**:793 (April 18) 1936.

Histories of a woman aged 55 years and three of her sons, aged 28, 24 and 21 years, are reported. All were afflicted with hypertrophic neuritis. One other male member of the family is said to have muscular atrophy. The maternal grandmother had wasting of the peripheral portions of all four limbs but was, as far as is known, the only member of the previous generation so afflicted. The onset of the illness in this family seems to be later than in the cases originally described by Dejerine and Sottas. The clinical manifestations, however, in all affected members of this family, which consisted of thickening of the peripheral nerves, symmetrical peripheral wasting of muscles, fibrillation, glove and stocking anesthesia and bilateral "pes cavus," are similar to those found in the syndrome of Dejerine and Sottas. The limitation of wasting to the forearms and the lower third of the thighs and the lack of progress of the condition beyond a certain degree of disability are also characteristics which were present in these cases.

BECK, Buffalo.

BILATERAL HERPES ZOSTER OF THE TRIGEMINAL NERVE. R. M. CAMPBELL, Lancet **1**:1066 (May 9) 1936.

Campbell states that, unlike herpes simplex, herpes zoster is rarely bilateral; it has been estimated that only thirty instances of this unusual condition have been reported. Of the one hundred and forty patients with zoster personally observed by Glauberson, only two showed involvement of the same or different segmental areas on the two sides of the body.

To a child aged 6 years diphtheria antitoxin had been administered before admission to the hospital for the relief of a profuse mucopurulent nasal discharge for three days. There was no previous illness. On admission to the hospital the only physical signs of note were: temperature 102 F., slight facial congestion, small patches of exudate on the tonsils and uvula and slight bilateral enlargement of the tonsillar glands. During the night the child had profuse diarrhea, the stools being green and frequent without visible blood or mucus. On the following morning the temperature subsided by crisis. Examination of cultures of material from the throat and nose failed to confirm the diagnosis of diphtheria.

On the second day circumscribed raised areas of erythema, each ½ inch (1.27 cm.) or more in diameter, were observed on the face. The eruption was strictly symmetrical on the two sides, being distributed on the forehead, nose, cheeks, malar regions and upper and lower lips. The symmetry of the lesions and their strict localization to the sensory area of the trigeminal nerve were striking. Small and large vesicles appeared on the erythematous bases by the following morning. At the same time, small shotlike glands were palpable in the posterior cervical chains. Rupture of the vesicles and crusting were completed by the eighth day. The cornea was not involved, and no lesions were visible in the mouth or fauces. No abnormality was found on general examination of the central nervous system. Scarring following healing of the herpetic areas was slight, and no sensory or motor impairment of function of the cranial nerves resulted.

Campbell states that the features in his case are compatible with primary infection of the gasserian ganglia by the unknown virus of herpes zoster.

WATTS, Washington, D. C.

PARALYSES ASSOCIATED WITH HEMOPHILIA. H. GÜNTHER, Monatschr. f. Psychiat. u. Neurol. **91**:33 (April) 1935.

In patients with hemophilia meningeal hematoma is observed with considerable frequency, but hemorrhages into the substance of the brain or spinal cord have not been conclusively demonstrated. Hematomas of the extremities may damage near-by peripheral nerves. Effusion of blood into the iliopsoas muscle, with involvement of the femoral nerve, is relatively common. This muscle must be especially susceptible to hemorrhage, since it is well protected from direct injury. The nerve is damaged by pressure of the extravasated blood, which may diffusely infiltrate the whole muscle. Three cases illustrating this type of involvement are reported briefly. In addition to local pain and swelling, there was paralysis or paresis of the quadriceps extensor femoris muscle, with absence of the patellar reflex and sensory impairment in the area of skin supplied by the femoral nerve.

ROTHSCHILD, Foxborough, Mass.

Treatment, Neurosurgery

MEDICAL AND SURGICAL ASPECTS OF CHARCOT JOINTS. SAMUEL EPSTEIN, Am. J. Syph., Gonor. & Ven. Dis. **20**:386 (July) 1936.

Orthopedic management of a Charcot joint is more important than antisyphilitic therapy. The orthopedic approach may follow radical (operative) or conservative (mechanical) lines. The types of operation vary with the site and extent of damage to the joint; thus, in an ankle with marked deformity osteotomy of the leg may correct the varus or valgus sufficiently to give considerable clinical relief. A Charcot spine may be stabilized with a massive tibial graft, or the spine may be fused. In Charcot toes the involved joints may be resected, the sinus tracts removed and the diseased bone amputated. In arthropathy at the knee arthrodesis is the operation of choice.

The conservative measures are designed to reduce pain and swelling and protect the joint from further damage. Such a regimen requires rest, immobilization (with splints, casts or braces), banning of weight-bearing movements, aspiration of fluid which may be distending the joint and use of local heat, preferably in the form of diathermy.

DAVIDSON, Newark, N. J.

INTOLERANCE TO TRYPARSAMIDE. ARTHUR G. SCHOCH, Am. J. Syph., Gonor. & Ven. Dis. **20**:408 (July) 1936.

While it is commonly thought that visual damage is the only complication of therapy with tryparsamide to be feared, Schoch suggests that an ill defined, antitonic effect is much commoner and less frequently anticipated. Three cases are reported illustrating the development of malaise, loss of weight and strength, nervousness and weakness. In each instance, the general health of the patient was improved after the abandonment of tryparsamide and its replacement by bismuth, neoarsphenamine or other antisyphilitic drugs. When tryparsamide therapy was resumed, the loss of weight and strength returned. This result of the therapy would appear to be exactly the opposite of the usual tonic effect of tryparsamide. No explanation for the phenomenon is offered.

DAVIDSON, Newark, N. J.

ACETYLCHOLINE IN TOBACCO AMBLYOPIA. H. CAMPBELL ORR, Brit. M. J. **2**:69 (July 11) 1936.

Acetylcholine as a therapeutic agent in tobacco amblyopia was suggested by the research of Parsons and others. In 1901 Parsons, as a result of experimental work on rabbits, suggested that the defect in tobacco amblyopia was due in part to two causes: constriction of the arterioles, which resulted in starvation of the macular area, where the blood supply is poor, or paralysis of the synapses in the

cone fibers or of the bipolar cells or both. In four cases of severe tobacco amblyopia treatment was by daily intramuscular injections of acetylcholine. The results in all cases were good. Recently, other observers have inclined toward the opinion that constriction of the arterioles is the primary cause of the amblyopia.

BECK, Buffalo.

THE HYPOGLYCEMIC TREATMENT OF THE PSYCHOSES. MANFRED SAKEL, Wien. klin. Wchnschr. **49**:1278 (Oct. 16) 1936.

The more dramatic dangers involved in treatment with insulin shock can now mostly be avoided, and it is relatively simple to find the dose of insulin which will produce coma in any one schizophrenic patient. The most difficult problem, however, for the physician who undertakes the treatment is to know when to terminate the hypoglycemia. The patient's behavior after termination depends largely on the state he is in when he is fed. In general, a patient in a state of hypoglycemic excitement is more likely to remain tense and restless after termination, and a patient in coma is likely to remain stuporous, quiet or subdued after termination. Or, as Sakel puts it, the patient tends to remain fixated in his psychotic state when hypoglycemia is ended. In reviewing his own wide experience of the past few years, Sakel attempts to formulate some general principles of management. The three groups of schizophrenic subjects—the paranoid, the stuporous and the catatonic—react differently to treatment and must be managed differently. Of these, subjects in the paranoid group respond most typically. A single dose of insulin once a day, protracted hypoglycemia and coma and termination after five or six hours lead in favorable cases to steady progress and improvement. The stuporous patient must, however, be activated first, and Sakel recommends termination during the period of reactivation, before coma sets in. When once the stupor is converted to a productive psychosis, the management must change accordingly. The catatonic and catatonic excited patients present the greatest difficulties in management. Sakel finds it advisable to give these subjects two or more doses of insulin a day and to terminate the hypoglycemia during somnolence or before actual deep coma sets in. Sakel emphasizes once more, however, that no scheme covers all cases, or any one case all the time. Only experience and constant observation, combined with psychologic tact and insight, can bring the best results.

JOSEPH WORTIS, New York.

HEMATOPORPHYRIN TREATMENT OF MELANCHOLIA AND ENDOGENOUS DEPRESSIONS. J. HÜHNERFELD, Ztschr. f. d. ges. Neurol. u. Psychiat. **154**:799 (Feb.) 1936.

The injection of small doses of hematoporphyrin resulted in rabbits becoming more lively, with increase in appetites. They also gained weight. Depressed patients became less retarded and more active. Hühnerfeld notes the stimulating tonic effects of the drug: The appetite improves; the skin looks better; there are gain in weight and increase in the number of red cells and hemoglobin. Hematoporphyrin increases the consumption and utilization of oxygen by the cells of the body and acts as a significant catalyst in cell metabolism. It increases salivation and relieves the gastro-intestinal symptoms usual in the depressed state. It even has a favorable effect on the annoying somatic sensations of these patients, as well as on the disordered sweating and defective oil secretion of the skin. It has also aided in restoring disordered ionic equilibrium in the blood. Alterations in the values for calcium and potassium sometimes disappear during the course of treatment. It has also been shown that the hyperglycemia sometimes noted in depressed states disappears under this treatment.

Hühnerfeld studied the effects of this therapeutic regimen in 90 cases of endogenous depressions. In the mild forms the drug can be given by mouth. In more severe types intramuscular injections alone are effective. The oral dose contains 5 mg. per cubic centimeter, and the injections, 2 mg. per cubic centimeter. Peroral medication is regulated so that from 500 to 700 mg. is given in from forty to sixty days. If the drug is given by mouth and by injection at the same

time, 60 mg. is given by injection for fifty days, and 300 mg., by mouth during the same period. It is emphasized that the injections must always be given intramuscularly. Subcutaneous injections result in changes in the skin, which, however, are usually transitory.

Of the 90 patients, 48 recovered, 30 improved and the condition of 12 was unchanged. Hühnerfeld denies that the improvement was really a spontaneous remission. The manner in which the patients improved is in favor of a significant effect of the drug on the course of the illness. The initial favorable effect on the somatic vegetative components of the clinical picture is noted. The psychomotor retardation disappears, followed later by disappearance of the depression. Conditions in which retardation and inhibition were marked were more favorable. The most unfavorable forms were those with intense anxiety and active delusional formations. Some of the patients showed a strikingly rapid response to the treatment. Most of them, however, showed improvement within from ten to fourteen days, while others were more resistant.

Including his own cases Hühnerfeld collected from the literature 346 cases in which this treatment was used; 156 patients (54 per cent) recovered; 86 (29 per cent) improved, and in 47 (17 per cent) no results were noted. Involutional melancholia reacted less favorably than the endogenous depressions of the cyclothymic variety. No significant complications of the treatment have been reported, though in advanced arteriosclerosis only half the dose is advised. The drug should not be used in cases of severe febrile disease and diseases of the liver.

SAVITSKY, New York.

Muscular System

THE METABOLISM OF GLYCOLIC ACID IN PROGRESSIVE MUSCULAR DYSTROPHY. ADE T. MILHORAT and VINCENT TOSCANI, J. Biol. Chem. **114**:461, 1936.

Administration of amino-acetic acid to patients suffering from progressive muscular dystrophy is known to be followed by increased excretion of creatine in the urine. Evidence suggests that glycolic acid can serve as a precursor of amino-acetic acid in the body. If this is so, its ingestion by patients should increase the output of creatine in a manner similar to that following the ingestion of amino-acetic acid. Milhorat and Toscani found a small increase in the output of creatine, which was considerably less than that produced by ingestion of an equivalent amount of amino-acetic acid. The results suggest that it is possible for man to convert glycolic acid into amino-acetic acid, but the amount transformed into the amino-acid is only a fraction of the amount administered.

PAGE, New York.

MYOGRAPHIC AND ELECTROMYOGRAPHIC STUDIES OF MYASTHENIA GRAVIS. DONALD B. LINDSLEY, Brain **58**:470, 1935.

Little is known of the cause and exact nature of myasthenia gravis. The reports on the beneficial results of treatment with amino-acetic acid by Boothby (1934) and Remen (1932) have pointed to a disturbance of creatine and creatinine metabolism. Nevin (1934), however, in a recent study of the phosphorus-holding compounds of muscle in myasthenia gravis, found them normal and concluded that there is no abnormality in the intrinsic chemical mechanism of muscular contractions in this disorder. He expressed the belief that alterations in creatine metabolism are secondary effects of the disease. The view that the transmission of excitation is somehow impaired in the region of the "myoneural junction" has arisen partly because of the exclusion of other factors and partly because of Edgeworth's (1930 and 1933) discovery that ephedrine is of value in the treatment of this disorder. Recent success in relieving temporarily myasthenic symptoms with physostigmine and the synthetic drug prostigmin (the dimethylcarbamic ester of 3-hydroxyphenyltrimethylammonium methylsulfate) has materially strengthened this view.

The present study is part of a general program of investigation of neuromuscular disorders by electromyographic methods and makes use of a technic for studying the electrical potentials of single motor units. Four patients presenting characteristic features of myasthenia gravis were studied. The responses of single motor units were recorded during voluntary contraction. Obvious differences were noted between the records and those obtained from the muscles of normal human subjects. The same regular rhythm was apparent, but there were wide variations in the amplitude of responses of single motor units, which were not characteristic of the records obtained from normal human subjects. The rhythm of responses of single motor units in all cases was as regular as that of normal human muscles, and there were no variations in rhythm which correlated with the fluctuations of amplitude. Even when one or two responses were absent, the regular rhythm of the unit was maintained and subsequent responses appeared "on time."

The four patients were all given injections of prostigmin, all exhibiting marked clinical improvement. Electromyographic records obtained immediately before the injection and again thirty minutes afterward showed that the responses of single motor units, which were irregular and often absent before, were consistently present and of quite uniform amplitude after injection of prostigmin.

The fact that the motor unit in myasthenia gravis maintains its regular rhythm, whether its electrical response is a fraction of its original amplitude or is absent, indicates that the motor neuron is functioning normally and conveying a regular succession of impulses to the muscle. Therefore, failure of response must be due to blocking the transmission of excitation at the "myoneural junction" or to a prolonged period of recovery of the muscle. The latter could hardly be the case, since the frequency of the response is from 10 to 13 per second, which would allow from 75 to 100 milliseconds between responses for recovery. In addition, a full-sized response often occurs immediately after one of diminished amplitude, without change in the duration of the interval between responses.

The characteristic irregularities of amplitude of the action potentials of the single motor unit and the associated weakness and fatigability of the muscles are due therefore to the failure of the nerve impulse to excite some or all of the muscle fibers controlled by the motor neuron. If the neuron sends branches to one hundred or more muscle fibers which compose a unit, irregularity in amplitude would seem to result from blocking excitation to a variable number of the muscle fibers supplied by the neuron. This would also result in a similar variation of tension.

After the administration of prostigmin, the action potentials are restored to a consistently uniform height, with the normal return of strength. Likewise, the myographic curves for tension in response to single and repetitive shocks through the ulnar nerve show a substantial increase after the injection of prostigmin. Since it has been shown that physostigmine prevents the inactivation of acetylcholine by blood esterase, the aforementioned results suggest strongly that acetylcholine or a related choline ester plays an important part in the transmission of excitation at motor nerve endings in skeletal muscle. SALL, Philadelphia.

PATHOGENESIS OF PROGRESSIVE MUSCULAR DYSTROPHY. ALEXANDER ROTTMANN, Ztschr. f. d. ges. Neurol. u. Psychiat. **153**:550 (Sept.) 1935.

The work of Kuré and his associates suggests that the nature of muscular dystrophy lies in a disorder in the autonomic nervous system. To investigate the plausibility of this theory Rottmann studied reactions of the skin to sweating, using 1 Gm. of acetylsalicylic acid in hot tea. Three sisters with typical relatively advanced progressive muscular dystrophy were used as subjects. Rottmann used the Minor method of daubing the body with iodine and starch before the diaphoretic was given. The resultant blackening of the hyperhidrotic surface contrasts with the powdery-white anhidrotic areas and facilitates recording of the results by photography. Extensive anhidrotic areas were found. Relative hyperhidrosis was evident in the skin adjacent to the areas with from diminution to

absence of sweating. This observation confirms previous studies of Foerster, Guttmann and List that compensatory hyperhidrosis appears in the neighboring skin whenever defective sweating exists in circumscribed areas. This accounts for the occasional paroxysmal sweating of patients with muscular dystrophy. Rottmann also states that in one case pilocarpine induced sweating of the volar aspect of the hand, notwithstanding the total anhidrosis following central diaphoresis. This observation supports the theory of the double innervation of the sweat glands in the hand by sympathetic and parasympathetic fibers.

Biopsy of the skin of the anhidrotic and hyperhidrotic areas revealed that in the affected skin the sweat glands were small, deformed and surrounded or replaced by fatty tissue. Only a few cells with well developed Golgi reticular apparatus were observed. Pigmentary deposits, not normally seen in the skin of the back, were noted in the basilar layers of the epidermis. The perivascular spaces of the cutis and subcutis were dilated and infiltrated with lymphocytes and plasma cells, with an occasional branching pigment cell. These cutaneous changes are somewhat analogous to the histopathologic condition of muscle tissue in the muscular dystrophies. These studies support the contention of the Kuré school as to the probable significance of disturbances of the autonomic nervous system in the pathogenesis of muscular dystrophy.

SAVITSKY, New York.

Special Senses

THE EFFECTS OF OCCIPITAL LOBECTOMY ON VISION IN THE CHIMPANZEE. K. W. SPENCE and J. F. FULTON, Brain **59**:35, 1936.

The fact that central vision appears to suffer relatively less than peripheral vision after unilateral destruction of the occipital cortex has long been known. Subtotal removal of the striate area in man is followed by impairment of the peripheral homonymous fields of the side opposite the lesion, the central or macular vision being more or less completely preserved. In other cases, in which larger lesions are involved, there is complete homonymous hemianopia of the opposite side, including the macular portion of the fields, with the vertical line passing through the point of fixation. For the most part, clinical examination in cases of injury to the occipital lobe has consisted of field determinations by perimetric methods and, in a few instances, of measurements of visual acuity. The latter, however, usually have been made with relatively crude methods and have been of little value in interpreting the function of the visual cortical centers.

In this communication Spence and Fulton studied the effects on visual acuity of occipital lobectomy in a cooperative adolescent female chimpanzee. The animal had been used extensively for two years in a comparative study of human and chimpanzee vision (Spence, 1934), during which stable standards for acuity had been established over a medium brightness range. This is the first recorded study of the results of occipital lobectomy in a chimpanzee.

Two successive cortical extirpations were made. At the first operation the entire left occipital lobe, including all the calcarine cortex, was removed. Determinations of visual acuity at four brightness levels were made between the seventh and the forty-third day after operation. A second operation involving subtotal extirpation of the right occipital lobe was then performed and visual acuity again tested. The Ives visual acuity test object was employed in the tests.

Removal of the entire left area striata resulted in slight, but constant, loss in visual acuity, ranging from approximately 5 to 15 per cent, at four brightness levels. After the second operation, which left the animal with only the anterior portion of the right area striata intact, there was complete failure to discriminate a pattern sixteen times as large as that discriminated in the preoperative tests. Rough testing of the visual fields suggested that right homonymous hemianopia resulted from the first operation, while the second spared only the extreme left peripheral fields, i. e., the temporal half-moon.

The relation of visual acuity to the nerve elements, both peripheral and central, is complex. The studies of Hecht (1928) and others have presented fairly clearcut

evidence that visual acuity is a function of the density or grain of the rods and cones. In support of this conclusion is the fact that visual acuity varies in different parts of the retina according to the density of the elements, being greatest in the macular area, where there is the greatest number of elements per unit area, and least in the peripheral regions, in which these elements are less dense. Thus, the effect on visual acuity of removal or destruction of any part of the visual cortical elements will depend on the nature of the relation of these structures to those of the retina. The effects on the fields of vision resulting from partial and complete unilateral occipital lobectomy have led to a conception of this relationship as involving a strict anatomic point to point projection of the retina on the visual cortex. This view successfully accounts for the cases of small, circumscribed scotoma resulting from limited lesions and for the various quadrantic and hemianopic defects resulting from larger partial and complete unilateral lesions.

This fixed, specific relationship has been objected to, particularly in the case of macular vision. The objections are based partly on the preservation of central vision which occurs sometimes in cases of supposed complete unilateral damage to the visual cortex. These cases of macular sparing are explained adequately on the basis of diffuse organization of the macula, so that the fibers from the various parts of each macula are distributed in a random manner to both visual cortical areas. The ablation of one of these areas would result in no loss of function of any portion of the maculae but only in reduction in the density or number of the elements throughout each total macula. The implication of this latter view for measurements of visual acuity is obvious. With the reduction in the density of the functional elements, which would presumably be decreased about one-half, as this proportion of the macular fibers is estimated to cross in the chiasm, a corresponding loss in visual acuity would be expected. This expectation was not realized in the present investigation. Further evidence contradicting such a view is the fact that there is no macular sparing in cases in which the optic tract itself is completely interrupted, thus showing that fibers from the temporal half of the macula do not cross over to the opposite hemisphere, at least not by way of the optic chiasm.

A somewhat different hypothesis put forward to explain these cases of macula sparing is that a portion of the visual radiation crosses to the striate area of the opposite hemisphere through the splenium of the corpus callosum. The results of the present experiment are not conclusive as regards this hypothesis.

The purpose of the second operation was to determine whether the macula of the chimpanzee is projected on the posterior portion of the striate area in the region of the occipital pole, as Poljak has demonstrated for the monkey. In this operation the posterior one-fourth, including the entire lateral surface of the right occipital lobe, was either damaged or removed. There was thus complete bilateral removal of the supposed macular cortical areas. In such a subject central vision should be nonexistent. The experimental tests of visual acuity and observations of field defects tended to confirm this expectation. Visual acuity was considerably below that to be expected of the macular region for even the lowest illuminations, while the visual field tests indicated that vision was present only in the extreme peripheral portion of the left field. This latter observation is also in agreement with the numerous studies of men which show that the far periphery of the visual field, the temporal half-moon, is projected on the anterior part of the area striata along the calcarine fissure, the only portion of the lobe left intact by the operation.

SALL, Philadelphia.

THE CEREBRAL REPRESENTATION OF THE RETINA IN THE CHIMPANZEE. S. POLJAK and REI HAYASHI, Brain **59**:51, 1936.

The results of investigations of the visual system may be stated briefly as follows: The optic nerve fibers originating in the periphery of the retina corresponding with the upper and lower quadrants of the retina terminate in the medial and lateral segments of the lateral geniculate body, respectively. The optic nerve fibers originating in the macula terminate in the large intermediate

segments of the lateral geniculate bodies. The most dorsal and ventral bundles of the visual radiation originate in the medial and lateral segments of the lateral geniculate body, respectively, terminate in the upper and lower lips of the calcarine fissure and correspond with the upper and lower extramacular quadrants of the retinas, respectively. The intermediate bundle of the visual radiation originates in the large intermediate segment of the lateral geniculate body, is placed between the "peripheral" bundles, is the longest of all and terminates in the posterior portion of the striate area, around the tip of the occipital lobe. This bundle and its terminal cortex correspond with the homonymous halves of both maculae.

Poljak and Hayashi studied the afferent visual system in a chimpanzee. The animal had a radical extirpation of the left occipital lobe and subtotal removal of the right occipital lobe and had been observed by Fulton (1936). In the left cerebral hemisphere there was complete absence of the striate area of Elliot Smith (field 17, Brodmann). As a consequence, the nerve cells of the left lateral geniculate body were completely degenerated, no trace of normal cells being left in any part of the nucleus. There was also marked partial degeneration in the pulvinar of the left thalamus due to the partial injury of the area periparastriata or fields 18 and 19. The left corpus of griseum praegeniculatum was normal. The right cerebral hemisphere showed a more restricted lesion, limited chiefly to the tip or pole of the occipital lobe. Study of the retrograde degeneration of the nerve cells in the right lateral geniculate body showed more complete degeneration in the sections closer to the caudal end of the lateral geniculate body, extending over almost the entire nucleus and sparing not even the large cells of the ventral layers. Only the tip of the lateral segment preserved a nest of approximately normal large nerve cells. Toward the middle of the nucleus the degeneration, while still occupying the bulk of the nucleus, became gradually narrowed by the increasing medial and lateral zones, in which the cells appeared normal or only more or less atrophic.

While the exact projection of the various peripheral and macular quadrants of the retina on the lateral geniculate body in the chimpanzee is not known, Poljak and Hayashi believe that a certain comparison with the geniculate projection in man and in lower monkeys, known from the work of other investigators, is permissible. They conclude that in the chimpanzee, too, the macular portions of both retinas are projected on the large intermediate segment, placed toward the caudal end of the lateral geniculate body, while the upper and lower extramacular quadrants are represented in the medial and the lateral segment, respectively, of the same nucleus. If this is correct, the portion of the lateral geniculate nucleus degenerated in this case corresponds chiefly with the hemimaculae, and the portions remaining normal correspond with the extramacular portions of the homonymous hemiretinas, including the monocular crescent. This, in turn, leads to the conclusion that the anterior portion of the striate area which lines the posterior and larger portion of the calcarine fissure (largely intact in this case) corresponds also with the extramacular portions of the retinas, or of the visual fields, respectively, whereas the portion of the striate area covering the tip of the occipital lobe and spreading over its posterolateral face, removed in this case, is the portion in which the hemimaculae, respectively, the centers of the visual fields, are represented.

This case shows that the assumption made earlier, and also recently, that the macula may be represented partly in the anterior portion of the striate area, or that the macula is diffusely represented, is ill founded. The large size of the degenerated segment of the lateral geniculate body, ample enough for the entire macula, even if its size is generously measured, speaks against the preceding assumption. At least, it appears that the anterior portion of the striate area, intact in this case, is in no way directly connected with central or macular vision.

The completeness of the degeneration of the nerve cells in the intermediate segment of the lateral geniculate nucleus disproves the assumption that any number of the nerve cells composing the lateral geniculate nucleus may be the so-called intercalated or associational elements, cells with a short axis-cylinder, of

Golgi type II. The same fact is also inconsistent with the view that some of the geniculate cells, especially the large cells, may send their axis-cylinders to the superior colliculi or elsewhere, and not to the cortex. It is more plausible that all geniculate cells, including the large ones in the ventral layers of the nucleus, since they disappear in consequence of the lesion to the occipital lobe, give rise to the axis-cylinders which terminate in the striate area.

The fact that the circumscribed lesion of the caudal end of the striate area produces a sharply delimited degeneration in the intermediate or macular segment of the lateral geniculate body once more disproves Monakow's concept, still adhered to by some investigators, that the macular fibers of the visual radiation spread over the entire territory of the striate area. The case reported by Poljak and Hayashi shows that the macular fibers have a well delimited area in the cerebral cortex, the posterior portion of the striate area, beyond which they do not reach.

SALL, Philadelphia.

VISUAL HALLUCINATIONS AND LESIONS OF THE VISUAL APPARATUS. J. LHERMITTE and J. DE AJURIAGUERRA, Ann. méd.-psychol. **94** (pt. 1) : 231 (March) 1936.

In this contribution to the problem of visual hallucinations, Lhermitte and Ajuriaguerra discuss briefly the hallucinations occurring in association with central paralyses of the oculomotor nerves ("peduncular hallucinosis"), those associated with lesions at the various levels of the visual radiation (vascular and traumatic lesions of the occipital cortex and tumors of the temporal lobe) and, particularly, the visual hallucinations occurring in patients suffering from various organic diseases of the eyeball—cataract, retinitis, glaucoma and atrophy of the optic nerve. The visual hallucinations occurring in cases of lesion of the eye are not different from those which occur without such lesions. These hallucinations may be represented by all the varieties of false visual perception known in psychiatry—from elementary sensations of fog, smoke, clouds or luminous rockets to fantastic and vivid visual images of extreme complexity. The hallucinations in question are purely visual and are unattended by auditory, olfactory or tactile hallucinatory components. In most instances the patients are not fooled by their visions; they identify them as hallucinations and readily distinguish them from reality. However, there are exceptions to the rule. The hallucinations may develop after the ocular disease has existed for a long time, and they may persist after the lesion of the eye has been cured. Generally occlusion of the eyes or development of complete or partial blindness does not prevent the appearance of hallucinatory images. In fact, in many instances the cessation of visual function (amblyopia) seemed to bring about the fantopsies. Lhermitte and Ajuriaguerra disagree with the theory which attributes the genesis of the hallucinations in such cases solely to disturbance of the photoreceptors in the retina, thus creating a state of abnormal excitation which, when transmitted to the intracerebral optic apparatus, leads in turn to a faulty cerebral elaboration of the retinal stimuli. The ocular lesion, they believe, plays a mere contributory rôle in the pathogenesis of visual hallucinations. Disturbance of the functions of the brain as a whole is essential. In many such cases neurologic signs of associated organic cerebral disease are shown. In many instances the hallucinations develop in relation to general infection and episodic cardiopulmonary disturbances. The authors conclude that a special constitutional tendency to project visual images outside the physical personality, coincident somatic disease, infection and associated localized or diffuse cerebral lesions are the etiologic factors which create a "hallucinatory state" and thus are responsible for the fantopsies which occur in some patients suffering from diseases of the eye.

YAKOVLEV, Waltham, Mass.

ISOLATED ABOLITION OF THE LIGHT REFLEX (ETIOLOGIC VALUE OF THE ARGYLL ROBERTSON SIGN): IV. NONSYPHILITIC FORM. H. LAGRANGE and A. M. LAGRANGE, Ann. d'ocul. **172**:729 (Sept.) 1935.

In this article Lagrange and Lagrange present a complete study of the recent literature on the Argyll Robertson pupil. Strictly, the Argyll Robertson sign

consists of: (*a*) absence of the pupillary reflex to light independent of the pupillary movements associated with accommodation and convergence, and (*b*) certain pupillary changes affecting the size and equality of the pupils and other changes in reflex pupillary movements. Lagrange and Lagrange believe that the semeiologic value of isolated absence of the light reflex should be considered the same as that of a syndrome in which absence of this reflex would have no value in the diagnosis of syphilis of the nervous system unless it was associated with other definite pupillary changes.

The isolated absence of the pupillary reflex to light was the most important sign discovered by Argyll Robertson. Loss of the pupillary reflex is a pathologic sign, which does not occur in normal subjects or in healthy elderly persons who have miosis. The isolated absence of the pupillary light reflex may or may not be associated with syphilis.

1. Association with syphilis: Whatever the origin or nature of the lesion in syphilis which causes the absence of the pupillary light reflex, the authors stress the importance of circulatory insufficiency, caused by involvement of the vegetative nervous system in tabes. In their opinion, this interpretation dominates the problem of localization. In syphilis the absence of the pupillary reflex to light may assume different clinical courses: (*a*) It may assist in a definite diagnosis of syphilis of the nervous system, but (*b*) it may suggest syphilis when this disease is not present.

(*a*) Pupillary symptoms which are considered "almost pathognomonic" of syphilis are: fixity, permanence, uniform diameter whatever the conditions of illumination may be, dissociation from accommodation and convergence, bilateral presence of the signs, an accompaniment of miosis, inequality, irregularity and absence of the pupillary response to painful and vestibular stimulation and incomplete dilatation after the instillation of atropine. The isolated absence of the pupillary reflex to light in association with these characteristics constitutes the true Argyll Robertson sign. In a small percentage of these cases it may be attributed to syphilis of the nervous system. Thus considered, the Argyll Robertson pupil is a rare sign.

(*b*) To this rare sign may be added isolated absence of the pupillary reflex to light, which may be associated with other clinical findings. However, it may occur without other complications; it may be associated with beginning atrophy of the optic nerve, with partial paralysis of the third, fourth or sixth nerve, as in cases of early atrophy studied by Argyll Robertson, with simple pupillary inequality, with other signs of syphilis detected during a general physical examination and with a positive Bordet-Wassermann reaction. Isolated absence of the pupillary reflex to light occurs in 38.3 per cent of cases of syphilis of the nervous system. Because of this fact, the sign is valuable when the rarity of the true Argyll Robertson pupil is considered.

2. No association with syphilis: Although the isolated absence of the pupillary light reflex is frequently observed in syphilis, it is not necessarily associated with this disease, as the reports of cases in this article demonstrate. The isolated absence of the pupillary light reflex is particularly valuable in the diagnosis of cerebral tumor involving the peduncle. In these cases it has localizing value. However, the danger lies in not recognizing a tumor as the possible cause and in making a diagnosis of syphilis.

In cerebral tumor the isolated absence of the pupillary light reflex is not always permanent, fixed and uniform, as it frequently is in syphilis. It has been seen to be momentary, varying in intensity, complete one day and partial another, unilateral and associated with mydriasis, and it may improve instead of becoming fixed. Doubtless, these rapid changes may be explained by transitory circulatory disturbances of an ischemic nature caused by intracranial hypertension, resulting in different pathogenic conditions but comparable to those caused by the permanent circulatory insufficiency which occurs in tabes.

However, the isolated absence of the pupillary light reflex may have the same characteristics that accompany the true Argyll Robertson sign. The anamnesis,

the clinical and serologic examinations and the knowledge acquired by study of the symptomatology and frequency of cerebral tumor are especially valuable in interpreting findings. The isolated absence of the pupillary light reflex may have a localizing rôle in the diagnosis of cerebral disease in the peduncular region. The isolated absence of the pupillary light reflex may be part of the symptomatology of infection of the central nervous system, such as herpes zoster. Isolated absence of the pupillary reflex to light has been observed in cases of oculo-orbital traumatism, which possibly suggests the peripheral origin of this sign. Studies of the syndrome of *"bradycorie,"* provisionally classified under the term "Adie's disease," describe a pathologic condition which is similar to the isolated absence of the pupillary light reflex and may be associated with neurosyphilis.

BERENS, New York.

CONGENITAL FAMILIAL OPHTHALMOPLEGIA. P. BONNET and L. PAUFIQUE, Ann. d'ocul. **173**:135 (Feb.) 1936.

Bonnet and Paufique report the case of a family in which the father and three children suffered from complete bilateral external ophthalmoplegia. The father, one of eleven brothers and sisters, was the first member of the family known to have the disease. Of the thirty-three members of the second generation, only the three children of this patient were affected. The signs were those of complete bilateral external ophthalmoplegia; ptosis was marked, and the eyeball was usually turned down and fixed. Rotary nystagmus was present, and convergence was paralyzed. Attempts to look up were followed by a quick movement of convergence, which was immediately replaced by nystagmus. Neither strabismus nor diplopia was present. Besides refractive changes, which varied in each patient, and changes in the fundus, which could not be studied properly because of the difficulties of examination, no other concomitant anomaly existed. The intelligence of the patients was normal.

BERENS, New York.

OPTIC NEURITIS OF DENTAL ORIGIN. JEAN SÉDAN, Rev. d'oto-neuro-opht. **14**:252 (April) 1936.

The mechanism of infection of the optic nerve from a dental focus is not exactly known. The majority of observers accept the theory of an arterial septicemic origin. The homolaterality of the ocular involvement has been explained by the assumption of a homolateral sympathetic reflex disturbance of the blood vessels, which creates a favorable soil for the transplantation of bacteria. Sédan reports the case of a woman who presented optic neuritis, a large central scotoma and slight mydriasis in the right eye. Vision had been reduced to 1/50. In spite of the fact that the Bordet-Wassermann test of the blood was negative, a course of mercury was ordered, the patient being referred first to a dentist for the purpose of having her teeth put in order. The dentist extracted a carious right molar with infected apex and canals and filled cavities. Four days after the extraction color perception returned, and rapid improvement of vision followed, reaching 7/10 in the course of a few weeks. Some peripheral scotoma remained. Mercurial treatment was not instituted.

DENNIS, San Diego, Calif.

Cerebellum and Brain Stem

REPORT: ABSCESS OF THE CEREBELLUM. Rev. d'oto-neuro-opht. **13**:727 (Dec.) 1935.

The need of precision and system in making a labyrinthine examination was stressed by Barré, who advocated the recording of the character and tempo of nystagmus, the extent and direction of deviation of each of the extended arms, the use of a plumb-line in making the Romberg test and the presence or absence of

"vestibular disharmony." The last-mentioned sign may be the first indication of cerebellar disease. Velter said that disturbances of associated movements of the eyes indicate a lesion of the posterior fossa and that deviation of the eyes to the side opposite the lesion is the most characteristic phenomenon of cerebellar abscess.

Halphen reported a case of a cerebellar syndrome complicating chronic sinusitis in which the Bordet-Wassermann reaction of the spinal fluid was strongly positive. The patient recovered promptly with antisyphilitic treatment. Another patient was operated on, and a large cystic arachnoid pocket was emptied; a relapse occurred after a month, and the patient died; autopsy revealed a large cerebellar abscess. De Martel said that many of the serious disturbances in cases of cerebellar abscess arise from obstruction to the circulation of the cerebrospinal fluid; he advised the occipital route as the method of choice in operation.

De Morsier discussed the difficulty sometimes encountered in differentiating a pyramidal and a cerebellar syndrome. Cerebral lesions simulating lesions of the cerebellum, according to van Bogaert, are located in the paracentral lobule.

Ody reported the case of a young man with severe headache, vomiting, emaciation, stupor and left hemiparesis, on whom a right mastoidectomy had been performed five months before; healing was apparently perfect. Two weeks before his admission to the hospital, infectious endocarditis had been discovered. A jacksonian convulsion ensued and was followed by complete left hemiplegia, which lasted three days. The following week the same sequence of events was repeated. There were no signs of cerebellar involvement; nystagmus toward the right was noted. Operation on the right temporoparietal region revealed no evidence of abscess. A third crisis supervened, with tonic convulsion, opisthotonos and deviation of the head and eyes to the right. After the seizure there were slowing of the pulse, stiffness of the neck and disturbance of respiration. In spite of the lack of evidence of disease in the mastoid, the old wound was reopened; the dura was exposed, and a subdural abscess was evacuated; the lateral sinus was not thrombosed. Rapid recovery followed. The cerebellar seizure was believed to be due to obstruction of the passages of Luschka and Magendie from edema of the hemisphere or tonsil; compression of the cerebral axis by the swollen organs accounted for the paralysis.

Roger cited the report of Puusepp of 331 cases of abscess of the cerebellum which has been overlooked by the reporters. In 264 of these cases the abscess was due to injury received in the World War; in 34 it was of otogenic origin; in 1 it followed a pulmonary abscess, and in 1, a fall on the head, without resulting demonstrable fracture of the skull.

Dereux reported the case of a man aged 50 who had a staphylococcic infection causing furunculosis, pulmonary abscess, left occipital osteitis and encephalitis of the cerebellum; three microscopic abscesses, not observed at operation, were seen at autopsy. Dereux maintained that by aid of tests for passivity (hypotonia of André-Thomas) this diffuse inflammation was revealed. Signs of disturbance of tonus often appear earlier than other signs. He questioned the statement that a cerebellar abscess can remain without symptoms until death.

Moriez observed a case of cerebellar abscess associated with psychosis. He attributed the psychosis to associated diffuse encephalitis. Signs of pyramidal involvement were present also and were explained by extension of the softening to the paracentral lobule.

Suñé y Medán reported a case of bilateral chronic otitis, with evident signs of abscess on right side of the brain. Right mastoidectomy and exploration of the brain revealed no abscess either of the cerebrum or of the cerebellum. Two days later paralysis of the left oculomotor nerve, adiadokokinesis and coma developed. The left mastoid was exenterated, and a large abscess of the cerebellum was evacuated. The patient recovered. Dainage by glass tube and dressings twice a day are advocated in cases of abscess of the brain.

Weill called attention to difficulties in respiration in cases of abscess of the cerebellum. A case in point was that of a man with coma and respiration of the Cheyne-Stokes type. Respiration ceased with the first whiff of ether and again on evacuating the abscess. Weill described also a case of dementia praecox associated with chronic otorrhea, in which an erroneous diagnosis of abscess of the brain led

to a futile operation. He warns that in an adolescent patient with chronic otorrhea accompanied by signs of obtusion, headache and emaciation, early manifestations of dementia praecox should be sought.

Portmann and Despons reported 4 cases of cerebellar abscess observed at autopsy. They expressed the belief that the diagnosis of an encephalic complication can be established only by a grouping of the symptoms noted from day to day. A single sign of meningeal or cerebellovestibular involvement is not sufficient for diagnosis. Cerebellovestibular signs are difficult to elicit because of the state of the patient or because the tests are not made systematically.

DENNIS, San Diego, Calif.

THE FUNCTION OF THE CEREBELLUM FROM A CLINICAL STANDPOINT. KURT GOLDSTEIN, J. Nerv. & Ment. Dis. **83**:1 (Jan.) 1936.

Although the cerebellum has been regarded as the coordinating organ for the maintenance of equilibrium, in recent years it has been considered less as an independent organ and more as one supporting cerebral innervations. Movements and posture voluntarily assumed by the whole organism are maintained by the cerebellum. Particularly is this true of flexion and adduction performances. There is on the side of the cerebellar lesion a tendency to abduction and extension, so that past pointing, deviation and similar symptoms are the expression of the same basic disturbance, namely, impairment of the function of supporting adduction and flexion. Decerebrate rigidity is an extensor rigidity which is diminished by stimulation of the cerebellum. Removal of the cerebellum increases decerebrate rigidity. Complicated activities as a rule are executed particularly by flexion and adduction movements. Actions requiring strength rather than accuracy are executed by extension and abduction movements, which are more closely connected with such subcerebellar centers as the red nucleus, the nucleus motorius tegmenti and the nucleus vestibularis. The positive symptoms of cerebellar lesions can be regarded as expressions of this abnormal reactivity of subcerebellar centers. This causes an abnormal turning of the organism or of the stimulated part of it toward the source of stimulation. The farther the stimulation is from the midline the more marked is the turning tendency. Normally one is able to hold his limbs in inconvenient positions; the patient with a cerebellar lesion, however, cannot maintain such a position steadily but tends to return to a more convenient posture. Certain abnormal postures are maintained by the patient with cerebellar disease because in them he feels best able to act or carry out movements.

In lesions of the cerebellum the innervation of the primary motor apparatus must be disturbed by lack of coinnervation of the cerebellum and by the impossibility of utilizing rightly the peripheral stimuli. These two factors are the main cause of direct symptoms of cerebellar involvement. Asynergia is based on injury of proper coinnervation of single muscles and muscle groups when individual parts of the cerebellum are destroyed. Goldstein believes that the facts about tonus are not yet clear. He has found well developed hypotonia to be rare. Tonus is maintained by different mechanisms of the nervous system—from the spinal cord to the frontal lobe, including the cerebellum. Tonus is always dependent on external stimuli. With lack of cerebellar coinnervation there may be hypotonia, because an important source of tonus is lost or injured. In chronic injuries Goldstein finds that hypotonia is not so easily demonstrable. It is mainly to be found with large circumscribed lesions of one part of the cerebellum. He considers that increase of innervation from the cerebellum must not be of the same kind as cerebral innervation but that more probably it resembles the innervation of the mesencephalic apparatus in being tonic. He concludes that one can understand the function of the cerebellum only as a part of the functioning of the brain as a whole, and the symptoms, only as performances of the brain deprived of a certain part.

HART, Greenwich, Conn.

Society Transactions

PHILADELPHIA NEUROLOGICAL SOCIETY

Regular Meeting, Jan. 22, 1937

FREDERIC H. LEAVITT, M.D., *President, in the Chair*

TREATMENT OF MYASTHENIA GRAVIS: REPORT OF 6 CASES. DR. MELVIN W. THORNER and DR. JOSEPH C. YASKIN.

From a review of the literature it would appear that in myasthenia gravis there is disturbance of the normal passage of impulses from nerve to muscle. The obstruction is probably at the myoneural junction and hypothetically may involve faulty metabolism of acetylcholine. There may be other factors in the etiology of myasthenia gravis which have not yet been established.

On the basis of the limited knowledge of the cause of this disease, prostigmin (the dimethylcarbamic ester of 3-hydroxyphenyltrimethylammonium methylsulfate) is the therapeutic agent of choice. It has proved valuable in treatment in all the 6 cases reported. This therapeutic reliability has proved so dependable that the response to prostigmin has come to be employed as a diagnostic procedure. Failure in a case of suspected myasthenia gravis to respond to prostigmin casts doubt on the diagnosis. In all the 6 cases there was prompt response to prostigmin therapy, while in 2 other cases in which the symptoms were suspicious but did not respond to the drug, organic disease of the central nervous system was found later. On the basis of experience of others with ephedrine sulfate, benzedrine was employed, so far as we know, for the first time, and was found advantageous in 3 of the 6 cases. The use of amino-acetic acid and potassium chloride and roentgen therapy produced no beneficial results.

DISCUSSION

DR. G. D. GAMMON: From the results with prostigmin that my associates and I have had at the University Hospital in the treatment of myasthenia gravis, we can bear out the statement of Dr. Thorner and Dr. Yaskin with regard to the drug. Every one reporting on the use of prostigmin has found it efficacious. English neurologists have been treating patients by this means for more than a year; they believe that it does not cure the disease but that it will maintain the patients in an improved state without bad effects from the drug.

The relief in myasthenia gravis from the use of prostigmin has importance other than its therapeutic value in the light it sheds on mechanisms underlying the disease. That prostigmin relieves both myasthenia gravis and curare poisoning suggests an analogy between the two conditions. It has also led to the hypothesis that myasthenia gravis is due to a defect in the neurohumoral transmission of nerve impulses to muscle. Prostigmin is held to potentiate the action of acetylcholine liberated at the nerve terminals by virtue of its property of inhibiting the serum esterase which normally hydrolyzes acetylcholine into less active choline. If the hypothesis is substantiated, the disease is the first instance, so far as I know, in which such a mechanism has appeared spontaneously. For that reason, the relief in myasthenia gravis from physostigmine and prostigmin assumes wide importance. I think it worth while to point out this fact, though I shall not discuss it further.

DR. WILLIAM L. LONG: The reasons that benzedrine would be effective must remain unknown until its true pharmacologic action is known. The drug is called sympathomimetic in that it is thought to resemble epinephrine, but it differs in its

action. If ergotamine is given first and then epinephrine, the blood pressure is lowered. Benzedrine, on the other hand, causes a rise in blood pressure after the use of ergotamine; so it is not certain that benzedrine should be called a sympathomimetic drug. Epinephrine has three hydroxyl groups, while benzedrine has none. Benzedrine is also more stable in the body and acts over a longer period; epinephrine, on the other hand, is destroyed quickly. The three hydroxyl groups are a point of attack for the body enzymes. It has long been known that the function of voluntary muscle is enhanced by action of the sympathetic nerves. Acetylcholine is liberated at the myoneural junction, and it may be that benzedrine, by stimulating the sympathetic nerves, liberates more acetylcholine and helps, therefore, to correct the defect at the myoneural junction.

DR. M. MOORE: I wish to corroborate the statements of Dr. Thorner and Dr. Yaskin concerning the efficacy of prostigmin in treatment for myasthenia gravis. In 6 cases, reported at the meeting of the American Neurological Association in June 1936 by Dr. Winkelman and me (Prostigmin in the Treatment of Myasthenia Gravis and Muscular Dystrophy, ARCH. NEUROL. & PSYCHIAT. **37**: 237 [Feb.] 1937), dramatic improvement was noted, particularly when the symptoms were marked. When a respiratory crisis is imminent or present, the drug may act as a life-saving measure.

A point well taken by Dr. Thorner is the value of prostigmin as a differential diagnostic agent. One of our patients whose condition had been diagnosed in various clinics, among other things, as neurosyphilis and who showed complete ptosis of one eyelid, responded immediately to prostigmin therapy. Our patients have not acquired tolerance to the drug, even after one and a half years of continuous treatment. We find that the parenteral administration of 1 cc. of the drug three times a day gives a more rapid and prolonged response than the oral use.

DR. E. SPIEGEL: I had the impression that it was assumed that benzedrine acts at the same place as prostigmin, i. e., at the myoneural junction. Since there exist accessory endings in skeletal muscle that are of sympathetic origin (Boeke) and since Orbeli has shown that this sympathetic innervation has to do with recovery of the muscle from fatigue, the question arises whether the effect of sympathomimetic substances may differ from that of prostigmin. Prostigmin may act on the myoneural junction, and benzedrine on the accessory endings. Thus, the synergic action of the two drugs in myasthenia gravis, as shown by Drs. Thorner and Yaskin, may be due to their action at different places.

DR. M. W. THORNER: It is not necessary to use the theories concerning acetylcholine to explain the action of prostigmin in myasthenia gravis. The directly stimulated muscle in the myasthenic patient responds normally. Abnormalities in the action potential picture are apparent when the muscle is stimulated by its nerve. When prostigmin is given, the action potential picture becomes normal. These data indicate that at least in part the action of prostigmin in myasthenia gravis is at the junction between the muscle and the nerve.

The reason that we entered into a discussion of the relationship of acetylcholine at the myoneural junction of voluntary muscle was to introduce methods of treatment utilizing potassium chloride and mecholyl. Our experience has been that neither of these agents is of any use in myasthenia gravis. From this standpoint one would think that the Dale hypothesis does not apply in this disease.

It is almost a truism to say that prostigmin is the agent of choice in myasthenia gravis, as so many corroborating reports have already appeared.

There is undoubtedly a thymic factor in myasthenia gravis, but as yet no therapeutic advances have been made in this direction. We have found no benefit resulting from roentgen therapy to the thymus, despite reports in the literature to the contrary. A potent extract of thymus gland given to myasthenic patients might have interesting results.

Our purpose in presenting this material was to visualize the chief modes of treatment in a controlled group and to compare their values.

SYPHILIS OF THE SPINAL CORD. DR. N. W. WINKELMAN.

The histories in a series of cases illustrate several types of syphilitic involvement of the spinal cord. The same general classification is used as that for lesions in the brain.

In the first general, or parenchymatous, type the clinical picture resembled progressive spinal muscular atrophy and amyotrophic lateral sclerosis. The differential diagnosis stressed the frequency of pupillary signs and an irregular type of involvement and progression. Cases were observed of atrophy of the muscles of the upper limbs and neck, without spasticity or atrophy of the lower limbs. Usually, serologic study gave ample evidence of the syphilitic nature of the condition. Treatment, if given early, usually produced an excellent result. In the late stages the effect of specific treatment was to stay the progress of the disease rather than to produce marked improvement. Histologic study in several cases showed an inflammatory and degenerative process involving the motor cells in the anterior horn, with mild chronic leptomeningitis and occasionally syphilitic involvement of blood vessels in the membranes and substance of the cord.

The second general, or interstitial, form of spinal syphilis includes involvement of the meninges and blood vessels, with secondary implication of the substance of the cord. Thus, it is possible to have primary meningeal involvement with secondary invasion of the cord in the nature of meningomyelitis or meningomyelitis gummosa. It is also possible to have syphilitic changes in the blood vessels within the meninges or cord and secondary softening due to vascular occlusion. Intramedullary gumma is rare.

The first case was that of a girl aged 4 years, who was seen at the Shriners' Hospital for Crippled Children, at the request of Dr. J. R. Moore. The child had been normal in all respects up to March 1936, when difficulty in walking began. By September marked spastic paraplegia had developed. When seen, the child showed spastic weakness of the lower limbs. Accurate sensory examination was impossible because of the age of the patient. Serologic study revealed the syphilitic etiology.

To illustrate the vascular type of syphilis, a case is cited in which after mild trauma there occurred evidences of involvement of the spinal cord, which progressed in attacks of apoplectic nature. Autopsy revealed a picture typical of chronic syphilitic vascular disease.

Other forms of syphilitic involvement of the spinal cord, including tabes dorsalis, are not discussed.

DISCUSSION

DR. E. SPIEGEL: I have had no practical experience with the purely parenchymatous form of syphilis of the spinal cord described by French authors. I saw a patient several years ago who died of pneumonia, six or eight months after syphilitic infection. This patient presented no clinical symptoms of syphilis of the central nervous system. Histologic examination showed marked proliferation of the glia of the posterior columns and only slight infiltration of the subarachnoid space and around a few vessels entering the posterior columns. Thus, in this case initial histologic changes were shown in the cord without clinical neurologic symptoms, which stresses the point that syphilitic infection of the spinal cord can appear at an early period before clinical symptoms are found.

DR. B. J. ALPERS: I wish to ask Dr. Winkelman what is meant by the term cerebrospinal syphilis.

DR. N. W. WINKELMAN: In answer to Dr. Alpers: Cerebrospinal syphilis is a clinical term which covers practically every form of syphilis of the central nervous system, except dementia paralytica and tabes dorsalis. From the histopathologic angle, however, differentiation can be made between the various forms of syphilis of the central nervous system. It is possible to distinguish meningeal syphilis, vascular syphilis, parenchymatous syphilis, focal lesions and granuloma.

As a rule, syphilis is not limited to any one part of the central nervous system. In spinal syphilis this general rule also holds. It is not infrequent for a patient with some form of syphilis of the spinal cord to have in the brain mild meningeal infiltration of round cells of the lymphocytic type, as well as an occasional blood vessel showing either the Heubner form of endarteritis or chronic syphilitic disease. It is also possible in many cases of spinal syphilis to have the earliest beginnings of dementia paralytica, particularly in the cornu ammonis.

I believe that "cerebrospinal syphilis" should not be used as a pathologic term but should be reserved for cases of syphilis of the central nervous system in which clinical symptoms of involvement of widely disseminated areas are present.

Cortical Innervation of Ocular Movements. Dr. N. Scala, Washington, D. C., and Dr. E. Spiegel.

This article was published in the December 1936 issue of the *Archives of Ophthalmology*, page 967.

Fracture Dislocation in the Region of the Atlas and Axis, with Consideration of Delayed Neurologic Manifestations and Roentgenographic Features. Dr. Gabriel Schwarz and Dr. Robert Wigton.

Dislocation and fracture of the first two cervical vertebrae have been accorded considerable attention in the literature. Almost all possible types of disturbance of the structures in this region have been reported. The typical cases of "broken neck" are easily recognized, although, unfortunately, these often fall into the group in which the outcome is fatal. In less severe trauma local signs may or may not be present, and neurologic signs may be less marked, or even delayed for weeks or months after the injury.

The following two cases warrant consideration because of the length of the latent interval, the absence of local signs and the consequent diagnostic problems presented.

Case 1.—A white woman aged 53 was admitted on Nov. 7, 1928, to the service of Dr. William Spiller in the Hospital of the University of Pennsylvania, with the chief complaint of weakness of the right leg. The patient had noticed difficulty in the use of the right lower extremity for about one year prior to her admission. Weakness and dragging of the right leg progressed slowly up to the time of admission. About three months before admission the patient had noticed difficulty in the use of her right hand. Five years before onset of these neurologic disturbances the patient had been thrown from a horse and had landed on her head on a rock pile. She had suffered no local symptoms of cervical injury. Physical examination revealed no disturbance in the cervical region. Neurologic examination revealed no abnormalities of the cranial nerves. Sensory examination gave normal findings. There were slight weakness in the right lower extremity and signs of involvement of the pyramidal tract, moderate in the upper extremities and more marked in the right lower extremity. Laboratory examinations gave normal results.

Dr. Temple Fay attempted to make an encephalogram. Only 67 cc. of fluid was obtained, and the patient complained of severe pain at the back of the neck during the procedure. Examination of the cervical region showed fracture dislocation of the atlas on the occiput. The odontoid process was fractured. The late Dr. Charles H. Frazier performed laminectomy in the region of the first and second cervical vertebrae. In his operative notes he stated that there was no evidence of constriction or anything to impede the passage of fluid or air into the cranial cavity. The dura and arachnoid seemed thickened and the arachnoid somewhat opaque. The spinal cord appeared to be normal. After operation the patient at first had slight improvement in the ability to use the right leg and slow but marked improvement in the use of the right hand. The last report in 1934 indicated that the neurologic manifestations had remained stationary since the slight postoperative improvement.

CASE 2.—A white man aged 34 was admitted in November 1934 to the service of Dr. William G. Spiller in the University Hospital, with the chief complaint of "dragging the right leg." The patient had first noticed limping six years prior to his admission. Difficulty with the use of the leg came on slowly and was at first noticed by friends. It progressed slowly during the following six years.

Physical examination revealed no abnormalities in the region of the cervical vertebrae. Neurologic examination revealed no disturbances in the cranial nerves, questionable disturbances of pain and temperature sensibility on the left side of the trunk and well marked signs in all four extremities of damage to the upper portion of the pyramidal tract. Laboratory tests gave essentially normal results. There was a suggestion of partial block in the Queckenstedt test. Roentgen examination of the cervical region showed forward dislocation of the atlas on the axis, with fracture of the odontoid process.

At first no history of an injury was secured. It was only later, after the roentgenograms had made the diagnosis certain and after further extensive questioning, that we determined that the patient had received an injury to the cervical region, at the age of 10 years, when he fell from a hay-loft and landed on his head. He was unconscious for a short time and on the following day found that his head was tilted to the right and that he was unable to move it. The condition was corrected by a practical nurse, merely by pulling and rotating the head to the midline. Since then, the patient had had no difficulty with movement of his neck.

Laminectomy was suggested, but the patient refused operative procedure; when last examined, he showed no roentgenologic or neurologic change.

Review of the literature reveals several recorded cases of delay in onset of neurologic symptoms following fracture dislocation in the region of the atlas and axis. The longest interval mentioned specifically was eight months, the average for all cases being three months. In addition, in the cases previously reported rapid or sudden onset and progression of the neurologic symptoms were presented. In our cases the delay was greater than that in any case reported in the literature. Furthermore, progress of neurologic symptoms was markedly slower than that previously described.

We believe that the neurologic picture in the cases cited may be explained on the basis of development of posttraumatic spinal arachnoiditis in the cervical region. We do not believe that the several causes of delayed neurologic symptoms, as mentioned by others in the literature, operated in these two cases.

We think, therefore, that in cases of disease of the spinal cord in which the etiology is uncertain abnormalities of the cervical region should be suspected, whether or not local signs of cervical injury are present, or neurologic signs accompany the injury, or even in the absence of a history of injury. Careful and, if necessary, repeated examinations of the cervical region should be made.

DISCUSSION

DR. TEMPLE FAY: I wish to add some details to the history in the first case. The patient complained of severe root pains, radiating in the area of the second and third cervical root segments on both sides. For five years prior to encephalography she had been considered neurotic because repeated roentgenograms taken by Dr. G. L. Chamberlain, in San Francisco, and roentgen studies by Dr. E. P. Pendergrass at the time of her admission to the University Hospital were reported as showing no fracture dislocation or disturbance in cervical alinement. There had, however, developed progressive loss of function of the right arm, with spastic hemiparesis on the right. After encephalographic localization in the upper cervical region, where signs of partial block were demonstrable, Dr. Pendergrass made careful measurements of the position of the skull in relation to the vertebra and established that the skull had been dislocated anteriorly on the vertebral column, so that the foramen magnum was carried anteriorly in such a way as to compress the cord in certain positions. I was present at the operation in which Dr. Frazier removed the posterior rim of the foramen magnum and

decompressed the lamina of the atlas. No gross injury to the cord was demonstrable, although there seemed to be a compression ring, and the usual space between the cord and the sternum magnum was obliterated.

I had the opportunity to examine the patient again in Washington, D. C., three months after the operation. She was then walking unassisted and was able to wear high-heeled slippers. Headache was less severe. The use of the right arm was greatly improved. She had danced a little at the President's inaugural ball. She had entered the hospital in a wheel-chair and formerly was unable to walk without a cane.

DR. M. W. THORNER: Last summer I learned that dislocation of the upper cervical vertebrae which is associated with acute symptoms of involvement of the cord is not necessarily fatal. The case was that of a man aged 40 who had suffered a trauma which was followed immediately by rigidity of the head on the neck and pyramidal tract signs. He refused hospitalization. In three weeks all signs and symptoms had disappeared.

DR. ROBERT WIGTON: It has been interesting to hear of the other cases mentioned. Clinically, this situation may be of more interest than is at first apparent.

DR. GABRIEL SCHWARZ: I wish to point out that in the first case reported the type of dislocation is extremely rare. In the literature I could find no instance of dislocation of the occiput on the atlas that was not caused by trauma so severe as to be fatal. This patient is the only one who has survived.

NEW YORK NEUROLOGICAL SOCIETY

Regular Meeting, Feb. 2, 1937

THOMAS K. DAVIS, M.D., *President, in the Chair*

VENOUS ANGIOMA OF THE SYLVIAN AQUEDUCT AND THE FOURTH VENTRICLE ASSOCIATED WITH INTERNAL HYDROCEPHALUS AND MENTAL DETERIORATION.

DR. CHARLES ROSENHECK.

Venous angioma has been of interest to neurologists, pathologists and neurosurgeons since Luschka first described cerebral angioma in 1854. The unusual and somewhat dramatic features in the case reported here concern a woman aged 58 who had been in failing health for five years; the final year of her life was characterized by deterioration not unlike that of Alzheimer's disease.

Postmortem examination revealed an angioma blocking the aqueduct and fourth ventricle, which interfered with the flow of cerebrospinal fluid, producing marked internal hydrocephalus and dilatation of all ventricular cavities. There was marked pressure atrophy of the frontal lobes, which no doubt was responsible for the mental dilapidation, although the architectural arrangement of the cells in the atrophied frontal areas showed no marked deviations from the normal. The correct diagnosis was not even remotely considered, and the postmortem observations were a surprise.

In most reported cases of angioma of the brain nevi of the skin, on either the face or the scalp, made possible the suspicion of a similar intracranial vascular anomaly. In the case reported here no such nevi were shown.

DISCUSSION

DR. CHARLES DAVISON: Although it is difficult to draw a sharp line between congenital telangiectasis and angioma, it is perhaps better to term the malformation reported by Dr. Rosenheck telangiectasis when it occurs in the region of the fourth ventricle and the aqueduct of Sylvius. By angioma one usually means a large tumor. Telangiectasis is not uncommon in the region of the fourth ventricle but usually causes no symptoms. A case in which symptoms are

produced is rare. Cushing cited a case, that of a psychoneurotic patient who after radical mastoidectomy had attacks of prolonged unconsciousness with symptoms suggesting arachnoiditis or a tumor of the posterior fossa. A suboccipital operation was performed, but no tumor was observed. After this procedure the attacks of unconsciousness ceased for eight years, except on two occasions. Then there suddenly developed severe headache, and the patient became comatose and died. Autopsy revealed telangiectases in the pons and medulla oblongata. A somewhat similar case of familial character was reported by Kufs. He reported multiple telangiectases of the skin in a man who died suddenly, at the age of 81. At autopsy numerous telangiectases were observed in the cerebral hemispheres, the pons and the liver. A daughter of this patient, at 17 years of age, had sudden alternating hemiplegia. From the clinical standpoint, Kufs concluded that the paralysis was due to hemorrhage from a pontile telangiectasis.

The first slide I am showing demonstrates telangiectases in the region of the fourth ventricle in a case in which there were no neural symptoms. The dilated channels are lined by a single layer of endothelial cells and a few collagenous fibers. I have seen this condition frequently in the region of the fourth ventricle or the aqueduct of sylvius, without obstructive signs.

The next slide is from the specimen Dr. Rosenheck sent me. This section shows the fourth ventricle with dilated venous channels in its floor, producing obstruction. Similar venous collections are seen in the region of the aqueduct of Sylvius. The structures anterior to this show dilatation of the entire ventricular system. In the next slide, a section from the fourth ventricle and aqueduct, the structure of the dilated channels can be seen better. Their walls are not fully formed and consist of a single layer of endothelial cells and a few collagenous fibers.

DICTAPHONIC REPRODUCTION IN A CASE OF DEPERSONALIZATION. DR. C. P. OBERNDORF.

In presenting reports of psychiatric conditions, psychiatrists have long been aware that the written word fails to convey an exact picture of the patient's utterances. I have been particularly impressed with this reportorial difficulty in a case of depersonalization, and I asked the patient if she would make a dictaphonic record. A satisfactory record resulted from the experiment.

I believe that dictaphonic records offer a new means of demonstrating psychiatric interviews, comparable to cinematographic records in neurologic conditions and surgical operations.

Such a record should be made only with the full cooperation of the patient. The success of the first experiment led to similar records from several patients suffering from difficulties in the category of depersonalization. These records have been used for teaching purposes and have the advantage of presenting verbatim what transpired between the physician and the patient. At any point during a demonstration the record can be interrupted, and explanations of a remark or the aim of the question can be made to the student.

An illustrative record is presented.

DISCUSSION

DR. ISRAEL S. WECHSLER: It seems to me that the method holds promise. When it is perfected and a sufficient number of records are accumulated, it may give a scientific basis to the studies made in the psychoanalytic room. I imagine that psychoanalysts will object to it, as it will in some measure desanctify the sessions. Perhaps if a certain number of records are accumulated, it will be possible to make statistical and other studies, which at present are not available.

DR. C. P. OBERNDORF: As to the point which Dr. Wechsler made: It would seem possible better to control the work which the initiate in analysis does with the patient if it is recorded, and the controlling analyst may be able to determine much more accurately than from the verbal report of the physician what has actually occurred at the session.

The record presented is not in any sense that of an analytic session. It is merely the record of a situation in the case of a patient who has been receiving treatment for a long time.

I can conceive that certain objections may arise—that perhaps this violates the confidence of the patient. Under no circumstances should a record be made unless the patient is aware that it is being made and gives consent unqualifiedly. As I mentioned in the original presentation, so far as I can see, making these records about five months ago has not in any way interfered with my contacts with the patient.

EXCISION OF THE SPEECH AREA WITHOUT RESULTANT APHASIA. DR. ISRAEL S. WECHSLER.

I shall describe this case for two reasons: First, I think it is unique, and, second, it gives me an opportunity to make a few remarks on aphasia.

Briefly, it is the story of a man aged 26 who is right handed and in whose family there is no sinistrality. At the age of 11 he was struck by an automobile and sustained a fracture of the left side of the skull; he was rendered unconscious and remained so for two weeks. Apparently he recovered perfectly; he finished public school, went through high school, and graduated from college at the comparatively early age of 20.

After graduation, in 1930, he began to have spells, which have gradually increased in frequency and severity, so that at the time he came to see me, in August 1936, he had attacks every few days or few weeks, sometimes several a day or on consecutive days. At first these consisted of twitching of the right side of the face. Later the right hand began to jerk, followed by similar movements in the right leg. Occasionally the right leg alone was stiff. As a rule the convulsions were generalized. The spells lasted from one to ten minutes. The patient was unconscious during these attacks, and the pupils were always dilated and fixed. He had complete amnesia for the attacks. During the past two years he began to have what may be described as déjà vu phenomena. These consisted of flashes of memory or of scenes, neither of which were quite clear. Sometimes he had only the déjà vu phenomena. Occasionally he performed automatic movements during the spells. He was not somnolent after the attacks and had no headaches.

In addition to the convulsive phenomena he showed two symptoms. One was a halt or hesitancy in speech. It was not a stammer, nor was it aphasia. He stopped for a fraction of a second, as if thinking of a word, and then went on. The other symptom was inability to concentrate and lack of interest which amounted to some degree of mental deterioration. Previously a brilliant young man with literary ability, he ceased to write with originality or fluency. He was intelligent; he attended the theater and carried on normal conversations, but he was hampered by slowness of thought.

In 1931 an encephalogram was made, and the left ventricle was seen to be drawn to the left. He made the rounds of practically every neurologist and neurosurgeon outside New York City; he saw physicians in Philadelphia, Boston, Montreal, the Mayo Clinic and Baltimore, and I think he consulted an eminent neurosurgeon in New York. All advised against operation, except Dr. Penfield, who in 1933 suggested exploration. The family and patient were told that if operation was performed on the injured speech area, aphasia would result. They therefore refused to consider surgical intervention. The patient also was psychoanalyzed for eighteen months in Chicago, in the vain hope that he might receive benefit, although it was known that he had a definite organic lesion.

My examination revealed only some inequality of the deep reflexes, which were stronger on the right side, and inequality of the abdominal reflexes, which were more marked on the left. Speech was somewhat hesitant; he had not quite a stammer and no true aphasia. He recognized and could name objects perfectly; he read and wrote well, and he played cards and other games.

The question of operation arose. Contrary to the advice given by other consultants, I proposed that operation be performed, and for a definite reason.

The argument was as follows: The patient has a lesion in Wernicke's zone in the left temporal lobe; if this region is the speech zone he ought to have aphasia; since he has no aphasia, this area is not the language area for him. Hence, removal of this part of the cortex should not result in aphasia. It was a bold syllogism and a risky conclusion; I said so to the parents, but I think the reasoning was sound. At any rate, I accompanied the patient to Montreal to consult Dr. Penfield. It was decided to operate. Dr. Penfield observed a depressed fracture and dura between the fractured bones which prevented union of the segments. He removed (August 1936) an area of cortex extending from the junction of the rolandic and the sylvian fissure to the supramarginal gyrus and from the lower parietal gyrus to the first and second temporal gyri.

The operation, which was performed with the patient under a local anesthetic, took six and one-half hours. Every part of the brain excised was previously stimulated, and no aphasia resulted from the stimulation. At the most anterior point (shown on the screen) stimulation brought about a convulsion. With this exception, the patient was perfectly conscious and spoke intelligently all through the operation. He was unusually brave and stood the operation well. After operation he had a stormy time for a few days, though he had no convulsions and no aphasia. In five and a half weeks he left the hospital. He has had neither convulsions nor aphasia since the operation, up to the present. Unfortunately, I have not seen him during the last three months. Therefore I cannot give a more complete report.

The first slide shows the scarred, exposed dura. Stimulation at the most anterior point of the scar caused a convulsion. The next slide shows the cortex removed. The lateral ventricle was opened purposely. The area removed was about 2½ inches (6.35 cm.) long by 1½ inches (3.81 cm.) wide and extended to, but not into, the lateral ventricle. After the operation there was a quadrantic field defect, due to ablation of some fibers of the visual tract. As can be seen, practically the whole so-called sensory speech area was removed on the left side of the brain. The motor zone and the island of Reil were left untouched.

As to the question of aphasia: All neurologists have been trained in theoretical and schematic views—namely, sensory and motor aphasia, various types of sensory and motor and cortical and transcortical aphasia, and a host of others. All these schemata have grown up since the days of Broca and, particularly, of Wernicke. It has seemed to me, as it has to others, that they are too complicated and that clinically the theory does not fit the facts. All know that there are preponderantly sensory and preponderantly motor aphasias, but one also recognizes how difficult it is to localize a lesion by means of aphasia. In fact, I believe, though many will take exception to this statement, that the localization of a lesion by means of aphasia alone is not only difficult but unreliable. I reported several cases (*J. Nerv. & Ment. Dis.* **59**:31 [Jan.] 1924), in each of which my associates and I were misled because we tried to localize a tumor by means of the old schemata.

It seems to me that for clinical purposes it would be better if one spoke of aphasia in simpler terms. I know there is considerable danger in trying to simplify a subject which is not altogether simple, but I believe it would serve a better purpose to consider language or speech and aphasia in terms of a reflex. One is warranted in saying that the speech mechanism consists of an afferent or sensory, an intercalated and an efferent arm. On the afferent or sensory or receptive side are auditory, visual, gustatory and tactual, speech. If one sees or smells a rose or feels its petals, the words, "flower" and "rose" come to mind, and one speaks them. On the efferent or expressive or motor side are written, spoken and gestural speech. Obviously, there may be disturbances in the association fibers. If one considers the problem from the point of view of a reflex, one can speak of aphasias of the afferent arm and those of the efferent arm. One knows, of course, that there are rarely pure types of efferent, or motor, or afferent, or sensory, aphasia. In sensory aphasia there is always some disturbance on the motor side, and in motor aphasia, some involvement of the sensory elements.

For purposes of localization, if one takes the rolandic fissure as a general landmark, one may assume that everything anterior to it is likely to be efferent, or expressive. Anything posterior and inferior has to do with the receptive, or afferent, side of language. Therefore, if there is disturbance of sensory, or receptive, speech, the lesion is postrolandic or infrasylvian or both. I am leaving out the island of Reil, which is perhaps the most important, as Marie and Moutier long ago demonstrated. If, in addition to the disturbance in the afferent side of speech, there is another sensory sign or symptom, the localization becomes the more certain. Thus, if there is a quadrantic field edefect or a déjà vu phenomenon or another sensory hallucination, one is sure to be dealing with a postrolandic or an infrasylvian lesion. If, in addition to the disturbance in motor speech, hemiplegia or a convulsive phenomenon of the jacksonian type exists, one knows that the lesion is anterior. In this fashion, one associates a series of phenomena which reflect the function of a series of arcs or afferent pathways, on the one hand, and that of a series of arcs or motor pathways, on the other. This, it seems to me, is better, at least for clinical purposes, than the complex schemata of aphasia or their metaphysical correlates. The objection to the view expressed is that it may seem to oversimplify a question which is far from simple. To this I offer the apology that I have not tried to discuss aphasia; I merely offer a suggestion as to localization.

To return to the case, which I believe is one of the rare instances on record in which so much of the speech area has been removed without resultant aphasia: Whether, despite everything that is known, the patient is potentially left handed or whether the right side of the brain took over the language function is difficult to say. There is some reason to justify the second supposition. It may be that the right side of the brain normally has something to do with language and is capable of taking over speech if the left side is impaired. This is a question well worth discussing and investigating. Certainly, the right side of the brain is not "silent."

DISCUSSION

DR. KURT GOLDSTEIN: This is an interesting case. The patient was said to be right handed, and one would expect that such an extensive lesion of the left temporal lobe would be followed by disturbances in speech; yet no disturbance of this function was found. Dr. Wechsler decided on the operation in spite of these possibilities. He did so because he thought that the patient should have had speech defects before the operation if the region in question was important for speech functions. This decision proved to be correct—the patient had no speech defect after the operation. With the present ideas about localization in mind, how can one explain that the patient did not experience any disturbances in speech? I believe it is possible. The idea that special speech functions are localized in circumscribed areas must be modified, especially the concept of the strict domination of one hemisphere for speech performances. Usually it is assumed that in right-handed persons the speech area is localized in the left hemisphere and vice versa. That is valid only in a general way. In an individual case the condition can be much more complicated. It may be difficult to decide from findings in the living person, as well as from observations on postmortem material, whether an individual patient is right handed or left handed, even with the best methods. It cannot be decided with certainty whether the left or the right hemisphere is predominant in a given person. The matter becomes especially complicated by the fact that in many cases both hemispheres seem to be important for speech (Goldstein, K.: Lokalisation im Grosshirn, in Bethe, A.; von Bergmann, G. Embden, G., and Ellinger, A.: Handbuch der normalen und pathologischen Physiologie, Berlin, Julius Springer, 1927, vol. 10, p. 656). The difficulty increases because in some cases the preponderance of one hemisphere is apparently valid for some functions, while other functions are dependent on both hemispheres. It has long been known that the dominance of one side of the brain is more definite for motor than for sensory speech. Permanent sensory aphasias usually result from lesions on both sides of the brain. There has also been a great deal of discussion as to whether the repetition of speech in right-handed persons is a function of the right hemisphere.

One is forced to assume that in Dr. Wechsler's case, despite the seeming right handedness of the patient, the right temporal lobe was exceedingly important for speech in general, as well as for the sensory reception. If the so-called speech area on the left side had been important for speech in this man, he would have had at least amnesic symptoms of aphasia, both before and after operation. These appear commonly in disease of this region. The absence of disturbance in word finding before the operation may be used as a special argument for the assumption that the left hemisphere was not important for speech in this patient. Similar cases are not rare. I can demonstrate this by a case which I observed several months ago at the Montefiore Hospital, in which I can give the clinical picture as well as the postmortem changes. It may show, at the same time, the complex situation with which one has to deal. The brain of a right-handed man disclosed gross softening in the left hemisphere, involving the entire first temporal convolution, the adjacent part of the parietal lobe, the auditory area and the island of Reil. The patient was able to speak and to understand spoken language. He was not able to repeat any word, nor could he find words for naming objects. Because of destruction of the auditory center and the island of Reil, there was no doubt that hearing and the understanding of speech were functions possessed by the right hemisphere. However, the function of the right hemisphere was apparently insufficient for word finding and repetition. One may understand this, for it is known from other clinical experiences that disturbances in word finding especially have a close bearing on a characteristic change in the personality which I have described as a change toward a more concrete attitude. This was developed in my patient in an outspoken manner. Such a change in personality, as found in other experiences, is to be observed especially in cases of lesion of the left hemisphere. In my case one can assume that the unaffected right hemisphere was sufficient to maintain some speech performances but not others, for these were closely connected with the personality and the personality was changed by the lesion of the left hemisphere. Further, one can understand the findings only if one takes into consideration also the total personality of the patient and the changes it may undergo.

Progress will be achieved only if one abolishes the idea of circumscribed localization of special functions, to which one is inclined to hold fast, more because of laziness than because facts support it. The symptomatology in a localized process is dependent not solely on the localization of the process but on many other factors which concern anatomic as well as functional conditions. As to the pathologico-anatomic changes: It has long been known that the symptomatology may differ according to the anatomic process—for example, whether the disease is a vascular lesion or a tumor. Different types of tumor give different symptoms.

Hughlings Jackson and von Monakow—men who did much for the clarification of the practical problem of localization—have demonstrated how the idea of localization of function is based on insufficient investigations of anatomic structure and analysis of symptoms.

In the same way, my work is directed toward a better description of facts, and it is on this basis that I reject the theory of the circumscribed localization of functions as it is presented in the so-called classic form. There is no question that different parts of the cortex have a different significance; however, all attempts at localization are too crude to permit real delimitation. Localization of function never means parallelism with a special performance. However, performances are always the result of the function of the whole cortex, to which function every part of the cortex contributes something—each part in a different way (Goldstein, K.: Lokalisation im Grosshirn, in Bethe, A., and others: Handbuch der normalen und pathologischen Physiologie, Berlin, Julius Springer, 1927, vol. 10, p. 672).

One must distinguish between localization of performances and localization of symptoms. The clinic is interested especially in the latter, and I have little reason to deny that one is often able to make a focal diagnosis on the basis of the

symptomatology, for I have often done so. For purposes of the clinic one's knowledge is sufficient, even if it concerns only the gross relationship between a gross clinical picture and a lesion of a somewhat limited part of the cortex. However, I believe that progress also in the clarification of this relationship will bring about greater practical success. One will be able better to view the facts and, especially, the importance of the change in total personality, which is derided by some authors. If the concept of the change in the total personality in some patients takes on meaning, it will become important for diagnosis (especially focal diagnosis) and therapy. (Demonstration is made of slides of the brain in the case described in the discussion.)

Dr. Samuel Brock: I hope that Dr. Wechsler will see that architectonic studies are made of the piece of excised brain. My aim in this discussion is to call attention to the defects in knowledge concerning normal speech. As the late Dr. Theodore Weisenburg realized, the complicated problems of aphasia can be solved only when one comprehends clearly the normal. The simple question of hemispheral dominance is an example. Is speech a function of one hemisphere in all persons, or is it sometimes a function resident in both cerebral hemispheres? Is the latter the case in the ambidextrous person? Again, to what extent can one hemisphere compensate for the other? Is one able even to foretell which is the dominant hemisphere? Does handedness help? Dr. Chesher told me that he observed recently a thoroughly left-handed man, 43 per cent of whose stock was left-handed, in whom operation was undertaken on the speech zones of the left hemisphere; severe aphasic disturbance followed. One would think that his speech areas should have been on the right side. In specific localizations one has been too thoroughly trained by diagram-makers—another bit of evidence of the strong tendency in human thinking to express conceptions in forms, or *Gestalten*. Small wonder that a revolt against diagrammatization has been in progress for years.

How variable are the extents of the so-called speech zones? They have not been defined satisfactorily. Has one any idea of the functional significance of the various layers of the cerebral cortex in speech? What is it that makes a person so sensitive to tone that he can detect and point out the source of a wrong note in a great orchestral potpourri of sound, while another man, just as intelligent, cannot carry the tune of the simplest musical phrase and cannot sing in tune or out? Similar observations and contrasts can be made in other fields, especially in that of reckoning. Think of the remarkable powers of lightning calculators and the visual memory possessed by masters of chess who can play a number of games simultaneously, though blindfolded. Form memories and remarkable capacities for spatial orientation must underlie these faculties. Some inkling of the nature of the disturbances that follow the defective recall of form memories has been given by the studies of Dr. Samuel Orton.

Normal man has a wide range of capacities in symbolic formulation and expression; yet one is still unable to make any neuro-anatomic correlations.

All realize the parts played by gesture, facial expression and the tone, timbre and pitch of the voice in speech; yet nothing is known of how these important tributaries join the main stream. One can tell a man to go to the devil with so much affection in the voice and gesture that he will love one ever after; on the other hand, the same words can be spoken with such venom that he will strike one down. What cerebral units produce the one result and what units the other? To say that corticothalamic and thalamocortical influences come into play is to speculate along lines which require a much more factual basis.

Since symbolic formulation and expression and their closely related emotional attributes are peculiarly human functions, one cannot study them in the lower species of animals. The cerebral cortex of man alone contains the answer to these vexing problems. There can be no doubt, too, that localization of various functional elements can be linked with certain parts of the hemispheres of variable extent. All this means one must study anew the normal and abnormal with more

precise clinical tests, with still finer histologic technics and with ever-growing insight into the nature of the problem. Otherwise, one will continue to be more or less speechless when one talks about speech.

DR. EARL C. CHESHER: I have no answer as to the reason that the patient whose case Dr. Wechsler described this evening had no difficulty in speech. I may cite 2 cases reported by Dr. G. Burckhardt (*Allg. Ztschr. f. Psychiat.* **47**:463, 1891). In both operation was performed with the expressed intention of inducing an aphasic state. In the first case 5 Gm. of gray matter was removed from the left temporal lobe, including the first and second temporal convolutions; eight months later the third frontal convolution on the left was removed, without resulting aphasia. In the second case the left supramarginal and the third frontal convolution were destroyed with a considerable part of Wernicke's zone, and no aphasia was noted. Both these patients were inmates of an institution for psychiatric patients and were operated on because of auditory hallucinations and excessive speech. Yet Burckhardt, following the diagrams, which were much in vogue at that time, thought it would be good therapy to destroy the speech mechanism. I presume he was considerably surprised when no disability followed.

In the case of the left-handed patient which Dr. Brock cited, the history of three generations of 23 persons disclosed 10 purely left-handed persons. The patient himself was purely left handed. The surgeons approached the left hemisphere, believing that they were keeping away from the language zone; they were considerably surprised when the man came out of the anesthesia mute and remained aphasic until his death a few days after operation. In another patient, a purely left-handed person, Dr. Penfield also removed the right temporal lobe with no resulting aphasia. A man aged 21 whom I saw with Dr. L. M. Davidoff, who had a history of grand and petit mal for seven years, had been hemiparetic since birth, the right side of the body being involved. The right arm was shrunken, as was the right leg. Some of the seizures were not unlike those in the case cited by Dr. Wechsler—that is, the right side of the body was mostly involved. Encephalography revealed that the left hemisphere contained a cyst with considerable scarring, and as the patient had never used the right hand but had always expressed preference for the left, Dr. Davidoff felt safe in approaching the left hemisphere. As a result of the incision and emptying the cyst, the patient was aphasic after the operation. What the relationship is between sidedness, motor patterns and the hemisphere in which language is integrated seems to be a dubious question. The cases of which I speak here and that of which Dr. Wechsler spoke I should regard as exceptions to the rule. Of several hundred cases of aphasia I have studied in the last five years at the Neurological Institute of New York, there was verified tumor of the brain in 163 (Chesher, Earl C.: *Bull. Neurol. Inst. New York* **4**:556 [April] 1936). The 163 patients were divided into three groups. The first group consisted of 88 patients with tumor in a specified anatomic area in the left hemisphere who were aphasic. In the second group were 66 patients with a verified tumor in a like anatomic area in the right hemisphere who had no aphasia. Both groups of patients were right handed. The third group was composed of 9 persons in whom the handedness was hard to settle; in other words, they had no consistent preference for one side. Of these persons 5 had a tumor in the left language zone, and 4, in the right hemisphere. All were aphasic. In other words, of the 163 patients 6 per cent constituted exceptions to the rule that the language mechanism is integrated in the cerebral hemisphere opposite the universally preferred hand.

One other possibility which I shall suggest concerns preexisting pathologic changes of long standing in the hemisphere in which the language mechanism is located. The adjustment to further injury, such as operative intervention, is made more promptly or more easily in these cases than when there is no preexisting pathologic change. My reason for suggesting this possibility can best be illustrated by citing the cases of 2 patients aged 14, in both of whom operation was performed on the language zone on the left side. Both were right handed. In one case the approach was made in order to reach an intraventricular tumor. The

result was a pronounced aphasic state, which existed until the boy's death, several months later. The other operation was performed to empty a cyst of Rathke's pouch, which had involved almost the entire left hemisphere and had stretched the cortex to the thinness of a few millimeters. The cyst was opened repeatedly. In each instance the patient showed only transient aphasia; in other words, the patient adjusted readily to the added insult, so that within a few days after the operation there was no disability. I cite these cases with the thought that pre-existing pathologic changes in Dr. Wechsler's case may have permitted a more ready adjustment of whatever functional mechanism takes care of language.

DR. JOSEPH E. J. KING: I have encountered several large abscesses of the brain—more often in the temporal than in the frontal lobe and more often on the left side than on the right—all of which were in right-handed persons. A little girl had an enormous abscess which began in the temporosphenoid lobe. When I operated, it had so increased in size that it occupied a temporal, frontal, parietal and occipital position. I removed nearly 8 ounces (236 milliliters) of pus; at least, it took more than 7 ounces (207 milliliters) of a saline solution to fill the cavity after the pus had been evacuated. It had perforated the skull in the temporal region, the defect in the skull being oval and measuring about ¾ by ⅝ inch (1.9 by 1.6 cm.). The outer covering, excluding the scalp, consisted of dura, a very thin bit of compressed brain substance and the wall of the abscess. The total thickness of these three structures was about ¼ inch (0.64 cm.). The patient was aphasic. All the patients who recovered were aphasic, either before or after operation or both. I know of no patient but one who now has the slightest speech defect. They talk and write well. One patient gropes about somewhat for a word but knows as soon as she has spoken the wrong word and corrects herself. In these patients I know that certain speech areas, as described in the textbooks, were already destroyed by the abscess and that more of these areas was removed at operation. In 3 cases especially, marked excision of brain cortex was made in the areas which are thought to control speech. During the World War I remember 5 patients at Fox Hills who had been shot in the left frontotemporosphenoid region; the wounds for the most part had healed. From the histories in the cases and from the record cards it was noted that a wide débridement had been made. Enormous destruction of the brain substance must have taken place. All these patients were completely aphasic and could not say a word. They were instructed daily. One man finally said just one word after eight months. He pronounced my name. I have seen this man several times since his discharge. He learned to speak well, although, to my knowledge, he was completely aphasic for eight months.

While Dr. Wechsler was showing the pictures of the extensive scar on the brain, I thought that this could not conceivably have formed in a short while. It could not have developed in a week or a few days. I did not understand whether or not the patient was aphasic after the injury, but there is no question that the injury which produced the scar was of long standing. I am of the opinion that the damage to the brain which was followed by formation of the large scar was of long duration. It is probable that the patient was aphasic immediately after the injury. In the interval between the original injury and the time of excision of the scar it is possible that some other portion of the brain took over the function of speech, as surely must have happened in the cases previously referred to.

Although the site of the scar in Dr. Wechsler's case must coincide with the speech centers and probably was the area which originally controlled speech in this patient, the speech center must have "migrated," so to speak, to another area, and the region from which the scar was excised no longer represents the speech center in this patient.

DR. JOHN E. SCARFF: My remarks are in line with what Dr. King has stated. A great deal has been said about the site of lesions, without stressing their character—I would stress the difference in the effects produced by an ablative lesion and those due to an irritative injury. In my experience it has seemed

that the location of the tumor is of less importance in the production of aphasia than the character. For instance, I have observed cases of a large cyst, a meningioma or an encapsulated abscess in various parts of the brain considered to be speech areas in which aphasia was not produced, and I have found it possible to incise almost any area in the inferofrontal region or in the temporal lobe in order to reach a tumor without producing aphasia. On the other hand, an infiltrating, even though small, glioma with edema and a sterile inflammatory reaction about it will produce marked aphasia. The same is true of the acute abscess, however small. It seems, therefore, that more cognizance should be taken of the part played by irritative (i. e., positive) processes, as compared with purely paralytic (i. e., negative) factors, in studying the mechanism of aphasia. From this standpoint, aphasia may prove to be a disturbance in rather than a pure loss of function.

Dr. Israel S. Wechsler: The subject is too large to discuss in one evening. This case does not demonstrate anything final for or against sidedness or specifically for or against localization. It is too exceptional to serve as proof. The fact is that the patient had a lesion in such an area that by all expectations it should have given rise to aphasia, and it did not. One can say only that in this case, since there was no aphasia to begin with, the reasoning that the speech area was not in the location of the scar was correct, and therefore one was justified in risking operation.

As to the change in personality, the patient became depressed over restriction of his social contacts with men and women. The occurrence of convulsions frequently put an end to budding friendships and worth-while associations. He became particularly sensitive over his inability to win over the ladies. Aside from being slow, his intelligence was not seriously impaired. What Dr. Scarff said is important. All have seen a large tumor, involving practically a whole hemisphere, give rise to few or no signs and symptoms. Evidently, it depends on what the lesion does to the brain—how much it destroys and how much it spares—and how rapidly or how slowly the process goes on. Dr. Brock's suggestion that the tissue removed be studied will no doubt be carried out. In conclusion, I trust that I have not been understood to speak against localization of speech areas. Surely, there are many types of localization of function in the brain. It is merely against schematic localization, against narrow conceptions of restricted centers, that one may argue justly. Nor do I think that in the case I described a solution of fundamental problems is offered. The case is important for its own sake and for the fortunate results of operation by a very skilful surgeon.

The Ayala Index: A Preliminary Report. Dr. Nathan Savitsky and (by invitation) Dr. Morris M. Kessler.

In 1923 Ayala suggested his so-called rachidian quotient as a means of ready differential diagnosis between an expanding lesion and other causes of increased intracranial pressure. The magnitude of the drop in pressure after the removal of a given amount of spinal fluid differs in cases of tumor of the brain and in those of acute and chronic hydrocephalus or meningitis without concomitant abscess. This index is computed by multiplying the ratio between the initial and the final pressure by a constant amount of fluid. This amount of fluid must be 10 cc. or more. One hundred and seventy-six consecutive cases in which increased intracranial pressure was shown have been studied from this standpoint: In all of 10 cases of abscess of the brain an Ayala index below 5 was shown, and in 6 of 7 cases, or 86 per cent, of otitic and sphenoid hydrocephalus an index above 5.5 was present. The index was found to be of greatest value in the differential diagnosis of these two conditions. In 84 per cent of cases of tumor of the brain the index was below 5.5; 42 cases of hypertensive vascular disease, in which focal signs were or were not present, were included in these series, and in 88 per cent the index was above 5.5. The occasional coexistence of

an expanding lesion and arterial hypertension presents a difficult problem. A low Ayala index is in favor of such a coexistent lesion. The clinical value of this index is enhanced by the simplicity of the technic. It merits further study.

DISCUSSION

DR. ISRAEL STRAUSS: In the November 1936 issue of the ARCHIVES OF NEUROLOGY AND PSYCHIATRY, in an article by Pollock and Boshes, entitled "Cerebrospinal Fluid Pressure," there occurs the statement that the Ayala rachidial quotient is of no value as an indication of the amount of spinal fluid but that "it may be of some clinical importance." Dr. Savitsky and Dr. Kessler have shown tonight that in my service at the Mount Sinai Hospital the Ayala index is of great value when properly used. I am certain that if this important method is universally employed, many papers will be written on its unreliability, for the reason that technical methods are often improperly carried out. If any one employing this method will follow exactly the technic described by Dr. Savitsky, there is no reason that it should not be found useful.

One other point that has been made by Drs. Savitsky and Kessler is likewise important—namely, consideration of the clinical picture. One cannot rely on any technical method, not even on the Wassermann reaction, in making a diagnosis. There are cases of syphilis, as all know, in which the Wassermann reaction is negative and yet the patient has syphilis; so it is necessary to use the technic under discussion in conjunction with the clinical signs and to exercise clinical acumen in judging its significance. When used properly, I am certain that the Ayala index as described by these two essayists is important and that it is a valuable addition to diagnostic technic.

DR. THOMAS K. DAVIS: I wish to ask whether any particular type of index has been noticed in the case of ball-valve tumor in the third ventricle.

DR. NATHAN SAVITSKY: In answer to Dr. Davis' question: We have observed a number of cases of intraventricular tumor, and in all a low Ayala index was shown.

DETROIT SOCIETY OF NEUROLOGY AND PSYCHIATRY

Regular Meeting, March 18, 1937

MARTIN H. HOFFMANN, M.D., *in the Chair*

OBSERVATIONS ON INSULIN HYPOGLYCEMIC SHOCK IN TREATMENT OF PSYCHOTIC PATIENTS. DR. L. C. GROSH JR., Ypsilanti, Mich.

This report includes information obtained from workers in the following institutions: the Harlem Valley State Hospital, Wingdale, N. Y., the New York State Psychiatric Institute and Hospital, the Worcester State Hospital and the Phipps Psychiatry Clinic, as well as from interviews with Dr. Joseph Wortis and Dr. Manfred Sakel. Among recent changes in technic is the omission of phase 4 (that of polarization) because during this step the patient is often left in an undesirable phase. This observation is related to Dr. Sakel's belief that the patient tends to be "fixated" at the psychic level present at the time of termination of the shock.

The various psychic changes produced by insulin hypoglycemia are: quieting of excitement, recession of the psychosis to a former level, uncovering of psychic traumas or conflicts and, especially, the appearance of lucidity. Ideal progress during treatment is shown when the improvement in the hypoglycemic phase tends to be continued during the rest of the day until evidence of the psychosis disappears entirely, except during hypoglycemia (reversed reaction). This reaction also may disappear eventually. This orderly progression is not found regularly. I have also observed the "activation of psychosis," in which the mentally and physically inert psychosis manifests awakening into activity.

I may mention the possibility that during hypoglycemic shock biochemical changes may produce mild generalized edema, which would explain in part the gain or loss of weight observed during therapy, and that the order of disappearance and reappearance of normal reflexes and the appearance and disappearance of pathologic reflexes during the development and recession of hypoglycemic coma may have some phylogenetic or ontogenetic significance.

Variations in technic and lack of agreement, which is possible both in diagnosis and in judging the degree of improvement, are matters of importance in comparing the results of various workers with the treatment. Apparently, those who use the most profound coma, in cases in which it is indicated, obtain in general the best results. The electro-encephalogram is possibly an objective means of detecting some of the significant changes that take place in the patient during the course of treatment.

Much more experience with insulin hypoglycemic shock therapy is required in the United States before a just opinion can be formed as to its warranted position in the field of therapy.

ENCEPHALOGRAPHIC FINDINGS IN DEMENTIA PRAECOX. DR. RALPH M. PATTERSON, Ypsilanti, Mich.

Encephalography was introduced at the Ypsilanti State Hospital, shortly after its opening in 1931, as an adjunct to diagnosis, particularly in cases in which organic change in the brain was suspected. My associates and I soon noted that there was considerable difference between our roentgenologic findings and those of a neighboring institution. Encephalography at our hospital, performed with the aid of narcosis, demonstrated more extensive subarachnoid markings than was the case elsewhere with the use of nitrogen monoxide anesthesia. Postmortem observations showed that we had been too liberal in diagnosing cortical atrophy on the basis of increase in subarachnoid markings without dilatation of the ventricles. Postmortem observations showed also that in the presence of moderate or large quantities of subdural air, producing asymmetry of the ventricles or apparent atrophy of the brain, the films were unreliable. In order to standardize our technic and interpretation of the findings, encephalography was performed in 49 cases of hebephrenic dementia praecox. Cases were selected in which there was no history of birth injury, trauma to the head or other illness which might have produced change in the brain. Narcosis was obtained by the use of barbiturate derivatives or tribromethanol in amylene hydrate. An effort was made to obtain complete drainage in each instance. In the majority of cases the single needle syringe method was used, with the injection of from 5 to 10 cc. more air than the volume of fluid withdrawn. In a few instances the closed two needle method was used, with the previous injection of 10 cc. of air.

In 5 instances the films were discarded because of the failure of one or both ventricles to drain, and in 5 other instances, because of interfering quantities of subdural air. One of the remaining 39 films presented findings unquestionably compatible with atrophy of the brain, in the form of widely dilated ventricles and absence of subarachnoid markings. In 1 instance the ventricles were asymmetrical. In 12 cases the findings were considered on the borderline, the subarachnoid markings being more extensive and prominent than the average and the ventricles larger than were considered normal. If organic changes in the brain were present in these 14 cases, one would expect to observe such changes on postmortem examination in more than one third of the cases of hebephrenic dementia praecox. Actually, complete postmortem study with histologic examination in 19 cases of dementia praecox revealed in only 2 instances organic changes in the brain of a chronic type which were not related to the terminal illness.

Conclusions.—1. Interpretation of encephalograms must take into consideration the technic and, particularly, the form of narcosis or anesthesia. 2. Interpretation must be conservative, with stress on the size, shape and symmetry of the ventricles, irrespective of subarachnoid markings, which may be increased, decreased or absent in atrophy of the brain and apparently increased in normal brains. 3. Since

our encephalographic findings are out of harmony with postmortem observations in dementia praecox, the interpretation of borderline conditions has been too liberal, and the diagnosis of atrophy of the brain should not be made unless the findings are obviously abnormal. 4. The term "atrophy of the brain" should be used rather than "cortical atrophy."

INCIDENCE OF PULMONARY TUBERCULOSIS IN SCHIZOPHRENIC PATIENTS DURING A PERIOD OF FIVE YEARS IN THE YPSILANTI STATE HOSPITAL. DR. WILLIAM A. SCOTT, Ypsilanti, Mich.

This study was undertaken to determine the incidence of pulmonary tuberculosis and schizophrenia in a new state hospital, in which schizophrenic patients would not have had prolonged hospitalization, as I thought that the length of the period might be a factor in the high incidence of tuberculosis in schizophrenia reported in the literature. In summarizing the figures collected, it was found that 162, or 5.1 per cent, of the total population of the hospital had tuberculosis. The schizophrenic portion of the entire group with active and healed tuberculosis was 122, or 3.9 per cent. The number of deaths in this group from all causes was 58, or 1.8 per cent, and from tuberculosis 33, or 1 per cent. In the nonschizophrenic group, tuberculosis occurred in active and healed form in 40 cases, or 1.8 per cent. Deaths in this group from all causes numbered 378, or 12 per cent, and from tuberculosis 19, or 0.6 per cent.

Review of the literature showed approximately similar ratios for the incidence of tuberculosis in schizophrenia. The mortality findings of other writers, however, appeared to be higher.

Conclusions.—(1) There is a higher incidence of tuberculosis in schizophrenia than in other psychoses; (2) prolonged hospitalization may be a factor, but the findings do not suggest this conclusion, and (3) no definite factor can be suggested, except the unusual affinity of both diseases for the same body type, plus the correlation of the two diseases, as pointed out by Luxemburger.

Book Reviews

Réactions Labyrinthiques et Équilibre. By G. G. J. Rademaker. Paper. 80 francs. Pp. 262, with illustrations. Paris: Masson & Cie, 1935.

This valuable monograph consists of an unusually complete account of observations on animals and patients with various lesions of the labyrinthine system. In the introduction Rademaker points out that up to the present all work on equilibrium has been nonphysiologic and of such nature as to show that the labyrinths act as organs in control of lack of balance rather than as organs controlling a balanced position of the organism in space. He defines the latter mechanism as one which initiates stabilizing reactions, i. e., reactions through which the line of the center of gravity remains within or is returned to within the limits of the base that sustains the mass. Objective rather than subjective tests of the labyrinthine function are used exclusively.

Rademaker states that there are three groups of labyrinthine reactions: (1) those caused by rectilinear vertical movements; (2) those caused by rotary movements, and (3) those caused by changes in the position of the labyrinths in relation to the force of gravity.

The first group (rectilinear vertical movements of the labyrinth) are demonstrated by allowing the animal to fall from a height feet first, head first and back first and is spoken of as the "reaction of the three falls." Supported change in position upward or downward—the "elevator reaction"—also comes within this class. In summarizing the results of these tests, it is apparent that labyrinthine reactions caused by rectilinear vertical motions produce in animals the following movements: In change of position from above downward, the neck stretches out and is carried dorsally; the extremities extend, and the toes spread. In accordance with the difference in conditions, the extension usually involves all four extremities and infrequently the forelegs or hindlegs alone. These reactions are probably otolithic rather than due to the action of the semicircular canals, although it is possible that both structures may be involved.

The second group of reactions result from rotation in three planes—about the craniopelvic axis, about the bitemporal axis and about the fronto-occipital axis. They are produced by rotation of the animal itself, and the changes occur in motions of the eyes, the head, the body and the extremities.

1. Craniopelvic rotation if made in a clockwise direction and viewed from the head end produces deviation of the two eyes to the left, followed by nystagmus to the right. The head also deviates to the left, and the body bends in such a way as to produce a concavity on the left. Response of the extremities is a secondary, indirect phenomenon. It is by these means that the labyrinths tend to neutralize the passive displacement of the eyes and head and to stabilize their position in space on a horizontal plane.

2. Rotation about the bitemporal axis if made backward produces a movement of both eyes toward the inferior border of the orbit, followed by vertical nystagmus toward the upper border, with the head moving ventrally and the pelvis and tail dorsally. There is also an increase in postural tonus and a backward shift of the four extremities. By these means the labyrinths tend to neutralize the passive displacement of the eyes and head and to stabilize their position in space in a sagittal plane.

3. Rotation about the fronto-occipital axis if made clockwise and viewed from in front produces a movement of the superior poles of both eyeballs toward the right, to be followed at once by rotary nystagmus, torsion of the neck which moves the head toward the right shoulder, rotation of the body, the back turning to the right and the left side becoming concave, an increase in postural tonus with extension and abduction of the left extremities, which move laterally and thus push the body to the right, and a decrease in postural tonus of the right extremities.

By these means the labyrinths tend to neutralize the passive displacement of the eyes and head and to stabilize their position in space in a frontal plane and in such a manner as to keep the bitemporal axis horizontal.

All these reactions are produced by rotating the animal itself and are initiated through the semicircular canals.

The third group of reactions, i. e., those produced by changes in the position of the labyrinths in relation to the force of gravity, are: (*a*) A vertical compensatory ocular deviation toward the superior orbital border, if the movement is around the bitemporal axis, and a compensatory ocular deviation which is rotary with the superior pole moving to the right, if the movement is clockwise around the fronto-occipital axis. Both these deviations are maintained until the head comes to rest in its new position. (*b*) Labyrinthine righting reactions brought about by lateral position of the head and those caused by displacement of the head about the bitemporal axis. (*c*) The tonic labyrinthine reflexes of Magnus and de Kleijn. This group of responses are probably otolithic, although a double initiation which includes the semicircular canals cannot be ruled out.

With these studies as a basis, Rademaker shows that in animals rotated on either the bitemporal or the fronto-occipital axis the postural tonus of the extremities on the left is mediated by the posterior vertical canal on the left and by the anterior vertical canal on the right and vice versa. It thus is apparent that the static position of an animal in space in either the sagittal or the frontal plane depends on the normal joint action of both labyrinths. By the ingenious application of certain of these tests to man, through the use of a tilting bed and rocking-chair, it is possible to show that the normal findings as measured in animals apply as well to man. Further check by means of prolonged observations on a group of eighty patients with various types of labyrinthine and cerebellar disease confirmed these findings as applied to physiologic abnormalities as well.

The final section takes up the question of so-called labyrinthine ataxia. Again, the same principles are applied and the same tests used. Studies are made on groups of animals in which bilateral labyrinthectomy with and without hemiextirpation of the cerebellum, bilateral labyrinthectomy and complete decerebellation with labyrinthectomy were performed.

With unilateral labyrinthectomy the resulting acute ataxia can be shown to be due principally to nonlabyrinthine activity. What symptoms there are become progressively better, until in the chronic state there are demonstrable only residual torsion of the neck, slight asymmetry of the action of the abductor muscles and slight ocular deviation. These all correspond with the signs seen in a normal animal which has been rotated about the fronto-occipital axis. If excision of one-half of the cerebellum is added to this condition, a more or less demonstrable alteration occurs in the threshold of excitation of the different centers that initiate motion.

Bilateral labyrinthectomy produces a variety of symptoms during the acute state, owing to absence of labyrinthine reactions and to difficulties due to modifications of symmetrical innervation of the muscles. These symptoms quickly pass, however, leaving an apparently normal animal, which walks, runs and plays with other dogs. It is only in a slight tendency to elevate the muzzle, with some exaggerated lateral swaying of the head while walking, that an abnormality is apparent, except under special circumstances. For example, the dog also has trouble standing on his hindlegs, going up and down stairs and jumping onto a height.

In man, swimming, flying and moving about in the dark or with the eyes closed produced difficulty. Such activity may prove even to be dangerous because of the patient's inability to substitute visual and proprioceptive stimuli for the absent labyrinthine reactions, with resulting inability to appreciate his position in space.

In totally decerebellate animals all the labyrinthine reactions are present. Certain apparent labyrinthine symptoms are due to the fact that the labyrinths are one of the sources of sensory stimuli which initiate motor responses that arise

in the cerebellum. If to the decerebellation, however, is added bilateral labyrinthectomy, the animal can neither stand nor walk freely. The additional loss of all labyrinthine reactions, plus the existing cerebellar asynergia and ataxia, markedly increases the disabling effect of the latter.

Practically the entire content of the book is devoted to descriptions of original experiments and clinical observations, the latter having been made at the Salpêtrière, with the assistance of Dr. Raymond Garsin. All descriptions are accompanied by moving-picture sequences, with many diagrams illustrating the principles involved, so that they are both convincing and easy to follow. An extensive bibliography is appended. This monograph should prove invaluable to those who are interested in the experimental or the clinical aspects of the physiology of the labyrinth.

Kriminalpsychopathologie und psychobiologische Verbrecherkunde. Second edition, enlarged and revised. By Dr. Karl Birnbaum. Linen, 18.80 marks. Pp. 304. Berlin: Julius Springer, 1931.

Lehrbuch der forensischen Psychiatrie für Aerzte, Juristen und höhere Beamte des Sicherheitsdienstes. By Dr. Rudolf Michel. Price, 13.50 marks. Pp. 274. Berlin: Urban & Schwarzenberg, 1931.

There is hardly a field—outside the combination of law and medicine—representatives of which would not want to show a lead in progressiveness and at least occasional attempts to get ahead of the times. Even in these days of crime commissions and wholesale condemnation of the legal and penal system, this country is only just beginning to parallel the books that for more than a generation have come from the camp of German psychiatrists. When one considers the rank and file of the best workers and students in psychiatry, one is impressed by the frank reluctance of the majority to enter the field that actually should appear doubly fascinating, touching both the science of disease, under the flag of ambition to heal, and the wisdom of the law, under the flag of justice.

Karl Birnbaum, up till recently the head of a leading hospital near Berlin for the treatment of mental disease, offers a criminal psychopathology and psychobiologic criminology, and Rudolf Michel, with thirty years' experience in medicolegal psychiatry at Graz, Austria, presents a textbook on forensic psychiatry. In continental Europe the examination and official report of the mental state of persons accused of crime are one of the important tasks of official psychiatry. With the journalistic exploitation of crime in this country for the promotion of sales of papers and revenue from advertisements—the idolatry of the "news" in the huge advertising enterprises—these problems are thrashed out before the public as long as the case is in the stage of mystery or public trial. It would not be news to give the final sifted and critical account. A few of the states have a beginning of organized work, but only rarely authoritative and final statements of what has been skimmed by the press. There have been several beginnings, like flashes in the pan, in courts and prisons to establish well considered records and accounts. There is a semblance of scientific and professional interest, but it is strongly under bewildering impressions of skepticism, which exploit such theories as "everybody is a potential criminal" or "everybody is more or less insane." Where laws cease to be organized common sense of the best informed and public opinion is guided by the flippant dealer in paradoxes and scintillation, it is a bit hard for plain facts and plain sense to find their place. Making a fetish of the cases of uncertain and undecided marginal nature, to the neglect of the study of what leaves few doubts, is a serious and dangerous method of creating false perspectives. Neither of these books makes its main capital of this favorite habit in the United States.

Birnbaum, actually led by practical interest, makes his presentation a psychobiologic one—to use the American term for the natural history type of the study of man and his functioning. In the text he starts from biopsychograms and psychobiograms, and while he offers first a discussion of the criminal pathologic

basis of symptoms and syndromes, followed by a "criminal pathology" of types of mental disease (processes and constitutions) and a consideration of the crimes and the criminal types from a psychopathologic angle (giving a special chapter to "the juvenile neglected" and one to the female criminal), he devotes the second part (pages 177 to 233) to the natural science problem of crime, under the headings of criminal anthropology (essentially the body form) and the psychobiologic aspect of the criminal, evidently in the sense of a bodily constitution and heredity and a peculiarity of the personality type (the author's "medical psychology" has no special heading for psychiatry). The third part (pages 234 to 276) deals with the penal aspects (the reaction to the crime, the prison, simulation and punishment), and the last part, with forensic problems (the questions of responsibility and the methods of expert reports which have to be given in a responsible written account open to cross-examination).

Michel begins frankly with the biologic make-up of the criminal as determined by law as the ethical minimum, but as studied with Lombroso's attention to the man and the attention of Ferri and Carofalo to the social factor, and the present day data of statistical study, the psychologic factors, the detection of crime and the forensic and penal aspects. There follows discussion of the laws, the mental disorders, their causes, the constitution and norms, the symptomatology, the methods of examinations and the various disease forms and their special relation to crime and prevention. The rules for the activity of the expert and the legal responsibility of the psychiatrist and a glossary of terms for nonmedical readers close the book. One cannot help envying the author for the natural and nondogmatic presentation of fact and theory and their application to the practical issues.

Even if the legal procedures differ in various countries, there is so much material of general concern and concrete helpfulness that these volumes are highly recommendable. They should also stimulate the promotion of more frequent studies in American practice.

Frigidity in Women: Its Characteristics and Treatment. By Eduard Hitschmann and Edmund Bergler. Authorized Translation by Polly Leeds Weil. Nervous and Mental Disease Monograph Series, No. 60. Price, $2. Pp. 76. Washington, D. C.: Nervous and Mental Disease Publishing Company, 1936.

The book opens with the statement that the female sex in general exhibits a deficiency in the field of sexual gratification. Frigidity apparently is a widespread biologic phenomenon, as in the animal kingdom males often possess some sort of clasping apparatus to hold the female during the sexual act. Such appendages become rudimentary when fully functioning extremities appear. The authors refuse to accept a pessimistic point of view in regard to women, arguing that in women there are well developed sex glands which secrete a variety of hormones. Sociologic factors, especially the manner in which girls are brought up, contribute a great deal toward subsequent frigidity. Various symptoms of frigidity observed by the gynecologist are discussed at length. The extreme threat to marriage which female frigidity presents is emphasized. The authors believe that frigidity, widespread as it is, becomes a definite threat to the institution of monogamous marriage and strongly urge treatment for this condition.

The authors take a broad view of sexuality, stating that a woman has not attained full development of genitality unless it includes child-bearing and nursing. In chapter II the development of female sexuality is described along orthodox freudian lines. The various types of frigidity are discussed in chapter III, with illustrations from cases in which analysis was made by the authors. To the prevention and treatment of frigidity the authors devote only two pages. They assert that in the majority of cases thorough psychoanalysis carries with it a favorable prognosis.